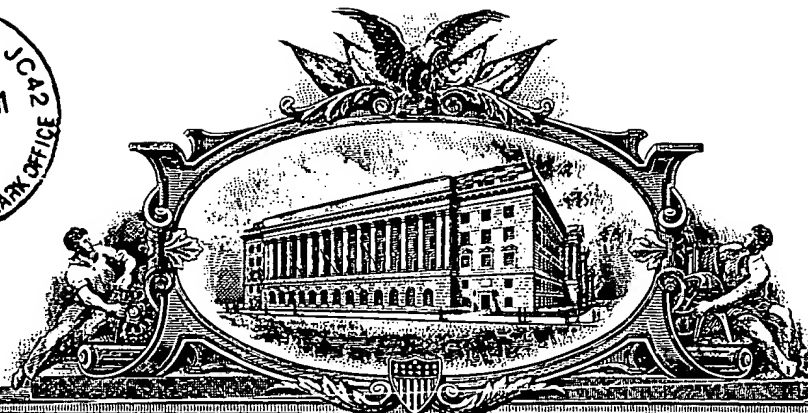




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APPLICATION NUMBER: 09/823,093

FILING DATE: *March 29, 2001*



By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

N. Williams
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Certifying Officer

04-02-01

A

02/29/01 JC962 U.S. PTO	UTILITY PATENT APPLICATION TRANSMITTAL (Large Entity) (Only for new nonprovisional applications under 37 CFR 1.53(b))	Docket No. 55778
		Total Pages in this Submission

TO THE ASSISTANT COMMISSIONER FOR PATENTS
Box Patent Application
Washington, D.C. 20231

Transmitted herewith for filing under 35 U.S.C. 111(a) and 37 C.F.R. 1.53(b) is a new utility patent application for an invention entitled:

PHARMACEUTICAL KIT COMPRISING MIDODRINE AS ACTIVE INGREDIENT

and invented by:

Poul BERTELSEN; Annete SKINHOJ; Peder MOHR OLSEN

03/29/01
JC929 U.S. PTO
09/823093

If a **CONTINUATION APPLICATION**, check appropriate box and supply the requisite information:

Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.: _____

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Enclosed are:

Application Elements

- ☐ Filing fee as calculated and transmitted as described below
- ☒ Specification having 113 pages and including the following:
 - ☒ Descriptive Title of the Invention
 - ☒ Cross References to Related Applications (if applicable)
 - ☐ Statement Regarding Federally-sponsored Research/Development (if applicable)
 - ☐ Reference to Microfiche Appendix (if applicable)
 - ☒ Background of the Invention
 - ☒ Brief Summary of the Invention
 - ☒ Brief Description of the Drawings (if drawings filed)
 - ☒ Detailed Description
 - ☒ Claim(s) as Classified Below
 - ☒ Abstract of the Disclosure

The PTO did not receive the following:
listed item(s) NO Amendment

UTILITY PATENT APPLICATION TRANSMITTAL
(Large Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.
55778

Total Pages in this Submission

Application Elements (Continued)

3. ☒ Drawing(s) (when necessary as prescribed by 35 USC 113)
- a. ☒ Formal Number of Sheets 24
- b. ☐ Informal Number of Sheets _____
4. ☐ Oath or Declaration
- a. ☐ Newly executed (original or copy) ☐ Unexecuted
- b. ☐ Copy from a prior application (37 CFR 1.63(d)) (for continuation/divisional application only)
- c. ☐ With Power of Attorney ☐ Without Power of Attorney
- d. ☐ DELETION OF INVENTOR(S)
Signed statement attached deleting inventor(s) named in the prior application,
see 37 C.F.R. 1.63(d)(2) and 1.33(b).
5. ☐ Incorporation By Reference (usable if Box 4b is checked)
The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under
Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby
incorporated by reference therein.
6. ☐ Computer Program in Microfiche (Appendix)
7. ☐ Nucleotide and/or Amino Acid Sequence Submission (if applicable, all must be included)
- a. ☐ Paper Copy
- b. ☐ Computer Readable Copy (identical to computer copy)
- c. ☐ Statement Verifying Identical Paper and Computer Readable Copy

Accompanying Application Parts

8. ☐ Assignment Papers (cover sheet & document(s))
9. ☐ 37 CFR 3.73(B) Statement (when there is an assignee)
10. ☐ English Translation Document (if applicable)
11. ☐ Information Disclosure Statement/PTO-1449 ☐ Copies of IDS Citations
12. ☒ Preliminary Amendment
13. ☒ Acknowledgment postcard
14. ☒ Certificate of Mailing
- ☐ First Class ☒ Express Mail (Specify Label No.): EL196832080US

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Total Pages in this Submission

Accompanying Application Parts (Continued)

15. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)*

16. ☐ Additional Enclosures *(please identify below):*

Request That Application Not Be Published Pursuant To 35 U.S.C. 122(b)(2)

- ☐ Pursuant to 35 U.S.C. 122(b)(2), Applicant hereby requests that this patent application not be published pursuant to 35 U.S.C. 122(b)(1). Applicant hereby certifies that the invention disclosed in this application has not and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication of applications 18 months after filing of the application.

Warning

An applicant who makes a request not to publish, but who subsequently files in a foreign country or under a multilateral international agreement specified in 35 U.S.C. 122(b)(2)(B)(i), must notify the Director of such filing not later than 45 days after the date of the filing of such foreign or international application. A failure of the applicant to provide such notice within the prescribed period shall result in the application being regarded as abandoned, unless it is shown to the satisfaction of the Director that the delay in submitting the notice was unintentional.

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UTILITY PATENT APPLICATION TRANSMITTAL
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Docket No.
55778

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Fee Calculation and Transmittal

CLAIMS AS FILED

For	#Filed	#Allowed	#Extra	Rate	Fee
Total Claims		- 20 =	0	x \$18.00	\$0.00
Indep. Claims		- 3 =	0	x \$80.00	\$0.00
Multiple Dependent Claims (check if applicable) <input type="checkbox"/>					\$0.00
BASIC FEE					\$710.00
OTHER FEE (specify purpose)					\$0.00
TOTAL FILING FEE					\$710.00

- ☒ A check in the amount of \$710.00 to cover the filing fee is enclosed.
- ☒ The Commissioner is hereby authorized to charge and credit Deposit Account No. 04-1105 as described below. A duplicate copy of this sheet is enclosed.
- ☐ Charge the amount of as filing fee.
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- ☐ Charge the issue fee set in 37 C.F.R. 1.18 at the mailing of the Notice of Allowance, pursuant to 37 C.F.R. 1.311(b).

Signature

Dated: March 29, 2001

Peter F. Corless (Reg. No. 33,860)
EDWARDS & ANGELL, LLP
130 Water Street
Boston, MA 02109

CC:

CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10)Applicant(s): **BERTELSEN et al.**

Docket No.

55778Serial No.
not yet assignedFiling Date
HerewithExaminer
not yet assignedGroup Art Unit
not yet assignedInvention: **PHARMACEUTICAL KIT COMPRISING MIDODRINE AS ACTIVE INGREDIENT**

I hereby certify that the following correspondence:

New Utility Patent Application

(Identify type of correspondence)

is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 in an envelope addressed to: The Assistant Commissioner for Patents, Washington, D.C. 20231 on

March 29, 2001*(Date)***Laura M. McGuire***(Typed or Printed Name of Person Mailing Correspondence)**(Signature of Person Mailing Correspondence)***EL196832080US***("Express Mail" Mailing Label Number)***Note: Each paper must have its own certificate of mailing.**JC939 U.S. PTO
09/823093
03/29/01

THE UNIVERSITY OF CHICAGO

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Midodrine kit PCT

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Pharmaceutical kit comprising midodrine as an active drug substance

This application claims priority to U.S. Provisional Application no. 60/203,783, filed May 12, 2000 and is incorporated herein by reference.

Introduction

- 5 The present invention relates to a method for treating mammals (such as, e.g., humans) in need thereof with a novel controlled release pharmaceutical composition for oral use containing midodrine and/or its active metabolite desglymidodrine together with a relatively fast onset composition of midodrine and/or its active metabolite desglymidodrine. The present invention also relates to a kit comprising a controlled
- 10 release composition, e.g. intended for administration once or twice daily, together with one or more relatively fast onset compositions for supplemental and individual administration.

- The invention also relates to a pharmaceutical composition comprising comprising
- 15 midodrine (ST 1085) or a pharmaceutically acceptable salt thereof and/or its active metabolite desglymidodrine (ST 1059) or a pharmaceutically acceptable salt thereof, the composition being adapted to provide midodrine and/or desglymidodrine in such a manner that a relatively fast therapeutically effective concentration of desglymidodrine is obtained after administration of the composition.

- 20 The novel controlled release compositions are designed to release midodrine and/or desglymidodrine after oral intake in a manner which enables absorption to take place in the gastrointestinal tract so that a relatively fast peak plasma concentration of the active metabolite desglymidodrine is obtained followed by a prolonged and relatively constant
- 25 plasma concentration of desglymidodrine. However, the patient may due to individual needs or because of activities during the day experience situations where an increase in the plasma concentration is needed for an optimal treatment regimen. Therefore, the patient may on an individual basis supply the controlled release composition with one or more administrations of a quick release composition or another composition providing a
- 30 relatively fast onset.

- The indications of midodrine include symptomatic orthostatic hypotension, orthostatic intolerance, symptomatic hypotension (e.g. hypotension associated with infections, the convalescent period, surgical operations, delivery, changes in the weather as well as what
- 35 is called "difficulties in getting started in the mornings"), as well as in the control of

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10 comprising an effective amount of midodrine and/or desglymidodrine.

15 substance is necessary to obtain a very fast relief from symptoms. If the constant base line plasma concentration was absent, it would be necessary to use a relative higher fast onset dose to reach the high therapeutically effective level. The high therapeutically effective level may be due to individual circumstances in the patient or may be a consequence of physical routines and/or the nature of the underlying disease. The

20 situations and symptoms are often well recognized and experienced by the patient himself. The kit according to the present invention is a superior tool for obtaining an optimal treatment with a minimum of active drug substance.

25 preferably once daily, i.e. a therapeutically effective concentration of desglymidodrine is maintained for a period of at least 10-16 hours followed by a wash out period of about 8-12 hours in order to avoid the well-known midodrine related side effect with respect to supine hypertension. In the present context a therapeutically effective concentration of desglymidodrine is defined as a plasma concentration of desglymidodrine of at least about
30 3 ng/ml such as, e.g. at least about 3.2 ng/ml, at least about 3.5 ng/ml, at least about 3.7 ng/ml, at least about 4.0 ng/ml, at least about 4.2 ng/ml, at least about 4.5 ng/ml, at least about 4.7 ng/ml or at least about 5 ng/ml.

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Controlled release midodrine compositions are known from the prior art, e.g. US-A-5,128,144 (Korsatko-Waabnegg et al.), EP-B-0 164 571 (CL Pharma Aktiengesellschaft) and AT-B-383 270 (Chemie Linz Aktiengesellschaft). However, in none of these documents are any compositions intended for less frequent administration such as, e.g., 5 once or twice daily and furthermore, there is no indication of absorption of midodrine (or its active metabolite) from the colon.

Disclosure of the invention

- 10 Midodrine is a prodrug, which is activated within the human body by an enzymatic hydrolysis to release the therapeutically active metabolite desglymidodrine. Desglymidodrine acts by a stimulation of α_1 receptors. Midodrine is used in the treatment of symptomatic orthostatic hypotension. Disorders causing orthostatic hypotension are e.g.,

15

Generalized primary autonomic failure

- ξ Pure autonomic failure or idiopathic orthostatic hypotension (Bradbury-Eggleston syndrome)
- ξ Pure autonomic failure with multiple-system atrophy or Shy-Drager syndrome
- 20 ξ Acute pandysautonomia (panautonomic neuropathy)
- ξ Familial dysautonomia (Riley-Day syndrome)

Partial primary autonomic failure

- | | | |
|----|---|---|
| 25 | ξ | Dopamine E-hydroxylase deficiency |
| | ξ | Postural orthostatic tachycardia syndrome (length-dependent autonomic neuropathy) |
| | ξ | Monoamine oxidase deficiency |
| | ξ | Pure vasomotor failure |

Disorders of idiopathic orthostatic Intolerance

- 30 ξ Postural orthostatic tachycardia syndrome
 ξ Mitral valve prolapse
 ξ Due to prolonged bed rest or space flight
 ξ Due to asthenic habitus

35 Disorders of the central nervous system

[illegible]

- ### Systemic diseases with autonomic neuropathy

- ### 30 Endocrine-metabolic disorders

- ξ **Primary and secondary adrenocortical insufficiency**
- ξ **Pheochromocytoma**
- ξ **Marked potassium depletion**
- ξ **Severe hypoaldosteronism**

- ξ Antihypertensive drugs (Δ -methyldopa, guanethidine, prazosin, β blockers)
- ξ Psychotropic drugs (phenothiazines, butyrophenones)
- ξ Antiparkinsonian drugs (Sinemet, Parlodel)
- ξ Vasodilator drugs (nitrates)
- ξ Certain illicit drugs (marijuana)
- ξ Thoracolumbar sympathectomy

- ξ Reduced intravascular volume
- ξ Acute and chronic blood loss
- ξ Fluid loss due to vomiting, diarrhea, diuretics
- ξ Gastrectomy with the dumping syndrome
- 15 ξ Salt-losing nephropathy
- ξ Altered capillary permeability
- ξ Impaired venous return
- ξ Severe varicose veins
- ξ Venous obstruction (late pregnancy)
- 20 ξ Reflex and pharmacologic vasodilatation
- ξ Muscle wasting and prolonged recumbency
- ξ Intrinsic cardiac disease
- ξ Myocardial infarct
- ξ Arrhythmias
- 25 ξ Restrictive pericardial/myocardial diseases

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- ξ Hyperbradycinnism
- ξ Chronic renal hemodialysis
- ξ Anorexia nervosa
- ξ Reduced aortic compliance
- ξ Mastocytosis
- ξ Baroreflex failure.

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After colon absorption a maximum plasma concentration of desglymidodrine is found to
35 take place at approximately 3 hours after application, i.e. t_{max} corresponds to approx. 3

hours. In contrast thereto, a t_{max} of about 1-2 hour for desglymidodrine is observed after oral intake of midodrine and the corresponding value for midodrine itself is a t_{max} of about 30 min.

- 5 The finding that midodrine is converted to the active metabolite before or during absorption from the colon is of importance with respect to the present invention. A further important issue is the fact that FDA has recommended that the latest dose of midodrine is taken not later than 6 pm for safety reasons, thus a wash out period through the night is desirable.

10

Based on the above findings and the therapeutic needs, the present inventors have developed a kit containing at least two different parts each containing midodrine and/or its active metabolite desglymidodrine. In the present context the term kit is intended to include

- 15 i) a package comprising at least a first and a second pharmaceutical composition, wherein the first composition is designed to release the active drug substance relatively fast in order to obtain a relatively fast onset of the therapeutic effect and the second composition is in the form of a controlled release composition (cf. a co-pending patent application by the same inventors) which is designed to give a release pattern as described below in
- 20 order to utilize the possibility of having the active drug substance absorbed not only in the upper part of the gastrointestinal tract but also during its passage through colon, the first and the second composition may be of the same kind, e.g. in the form of tablets or capsules or they may be in the form of two different types of pharmaceutical compositions e.g. the first composition may be in the form of plain tablets or a nasal spray and the
- 25 second composition may be in the form of controlled release tablets or capsules, and
- ii) a pharmaceutical composition which include a first and a second part, wherein the first part is designed to release the active drug substance relatively fast in order to obtain a relatively fast onset of the therapeutic effect and the second part is a controlled release part (cf. a co-pending patent application by the same inventors) which is designed to give
- 30 a release pattern as described below in order to utilize the possibility of having the active drug substance absorbed not only in the upper part of the gastrointestinal tract but also during its passage through colon, and the first and the second part are presented in the form of a single composition such as, e.g. in the form of a tablet, a capsule (e.g. containing pellets which may be the same or different), sachets, powders etc

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1. an initial rise in plasma concentration until a peak concentration is reached (in the present context "a peak concentration" is intended to mean a peak value, a shoulder value or a plateau value in the concentration),
2. a relatively constant plasma concentration of desglymidodrine for approximately about 4.5-14 hours such as, e.g., about 5-14 hours, about 6-14 hours, about 7-14 hours, about 8-13 hours, about 8-13 hours, about 10-14 hours, about 10-13 hours, or such as, e.g. for at least about 4.5 hours, at least about 5 hours, at least about 6 hours, at least about 7 hours, at least about 8 hours, at least about 9 hours, at least about 10 hours, or at least about 11 hours. In some case, the constant plasma concentration of desglymidodrine may last for at least about 12 hours, at least about 13 hours or at least about 14 hours,
3. a decline in plasma concentration with a half-life of e.g. about 3-4 hours to avoid supine hypertension but other half-lives may also be acceptable e.g. reflecting a continuous release of midodrine and/or desglymidodrine from the composition.

Compositions according to the invention are therefore designed based on the following principle; the term "part" is intended to include a separate part within the composition (the composition may contain pellets of e.g. two different types, or an integrated element of the composition, e.g. a multilayer tablet):

1. The composition contains a part intended for relatively fast release of midodrine and/or desglymidodrine
2. The composition contains a part intended for prolonged release of midodrine and/or desglymidodrine, and the prolonged release is intended to last for at least about 7-8 hours.
3. The composition contains a part intended to release midodrine and/or desglymidodrine relatively fast when the composition (or the disintegrated parts of the composition) reaches the colon, i.e. about 6-10 hours such as, e.g., about 8 hours after oral administration.
4. The release of midodrine and/or desglymidodrine from a composition according to the invention is terminated at the most about 12-16 hours after administration in order to obtain a wash out period during night.

In one aspect the kit according to the invention comprises a controlled release pharmaceutical composition for oral use comprising midodrine (ST 1085) or a

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the composition being adapted to release midodrine and, when present, desglymidodrine
5 in such a manner that a relatively fast peak plasma concentration of desglymidodrine is
obtained and that a therapeutically effective plasma concentration of desglymidodrine is
maintained for at least about 9 hours such as, e.g. at least about 10 hours, at least about
11 hours, at least about 12 hours, at least about 13 hours, or at least about 14 hours.

15 As mentioned above, it is important to keep the plasma concentration at a relatively constant level and, therefore, the plasma concentration of desglymidodrine after administration of midodrine and/or desglymidodrine is preferably maintained at a therapeutically active level for about 5-16 hours, such as, e.g., about 6-16 hours, about 7-16, about 8-15, about 9-15, about 10-15, about 11-14, about 12-14 or about 13, or for at

20 least about 5 hours, at least about 6 hours, at least about 7 hours, at least about 8 hours, at least about 9 hours, at least about 10 hours, at least about 11. hours, at least about 12 hours, at least about 13 hours, at least about 14 hours, at least about 15 hours or at least about 16 hours.

30 It should be noted that the initial fast release from the controlled release composition may be supplemented with or replaced by a separate fast onset composition (i.e. a first composition of the kit) resulting in a peak plasma concentration within the period stated for the initial rise in plasma concentration. A separate fast onset composition gives a flexibility with respect to the dose administered, i.e. if needed a relatively low or a
35 relatively high dose of the active drug substance may be administered dependent on the

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patient's needs. Thus, in other aspects the invention relates to such relatively fast onset compositions.

In principle, relevant active drug substances for use in a composition according to the invention are any drug substance for which a dissolution pattern as described below is of relevance. The most interesting drug substances in this respect and with respect to treatment of orthostatic hypotension and urinary incontinence are the prodrug midodrine and its active metabolite desglymidodrine. In a preferred aspect, a composition according to the invention includes midodrine alone, desglymidodrine alone, or a combination of midodrine and desglymidodrine. Of course such compositions may also contain other active drug substances, if relevant.

Generally, after oral administration of a composition according to the invention containing midodrine, a peak plasma concentration of midodrine is obtained 15-90 min after oral administration. Moreover, the plasma concentration of midodrine after oral administration is maintained at a relatively constant level for about 0.7-4 hours such as, e.g. at least about 0.7 hours, at least about 1 hour, at least about 2 hours, at least about 3 hours, or at least about 4 hours.

To this end, the term "relatively constant" is intended to mean m is $m \pm 60\%$, such as, e.g., $m \pm 50\%$ or $m \pm 40\%$ and wherein m is the plasma concentration in ng/ml and monitored in a healthy person. The determination of the "relatively constant level" is performed as described in Example 15 herein.

The relatively fast onset compositions in a kit according to the invention may be in the form of tablets such as, e.g. conventional tablets, melt tablets, coated tablets, buccal tablets, capsules, sachets, drops, dispersions, solutions, emulsions, suspensions, gels, hydro gels, nasal compositions such as, e.g. nasal spray or nasal powder compositions, compositions for pulmonary administration such as, e.g. inhalators, chewing compositions such as, e.g., chewing gum, etc. Especially suited compositions for a fast onset is compositions in fluid form and in the form of nasal compositions as well as quick release tablets.

In the following further details on a controlled release composition of the kit according to the invention is given.

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Examples on relatively fast onset compositions are illustrated in the Examples.

Dissolution requirements

5

As described in the following, a target plasma profile and release profile can be designed for the controlled release composition or the controlled release part of the kit comprising midodrine and/or the active metabolite desglymidodrine.

- 10 Based on our knowledge of the plasma profile of a midodrine solution and obtained C_{max} values for inactive midodrine and active metabolite desglymidodrine after tablet administration a target *in vivo* profile has been estimated (Figs. 1 and 2).

- 15 The target profile is based on the findings discussed above and the assumption that it would be preferable to have a fast onset of action and a relatively stable plasma level for 8-11 hours and thereafter to eliminate the drug during the night phase to avoid supine hypertension.

The presumptions made in estimating this target profile were:

20

- i) a fast peak and an effective concentration of the active metabolite for approximately 14 hours are desired from a therapeutic point of view (FDA recommendation: latest dose at 6 pm),
- ii) that the first fraction of the composition should have an absorption rate similar to
25 that of plain tablets,
- iii) that the peak concentration should not be higher than the peak concentration observed after administration of 33% of the total dose in the form of a plain tablet,
- iv) that the plateau level for midodrine should last for approximately 8 hours and for desglymidodrine for approximately 11 hours,
- 30 v) that the drug reaches colon after approximately 8 hours,
- vi) that midodrine is absorbed in the colon with a t_{max} of 3 hours (desglymidodrine) compared to a t_{max} of ½ hour (midodrine) when absorbed in the small intestine,
- vii) that midodrine will not be measured after the colon absorption as midodrine but only as desglymidodrine,
- 35 viii) that t_{max} of desglymidodrine will appear 1 hour after oral administration of midodrine,

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- 5 Based on the fact that midodrine plain tablets are dosed from 2.5 mg - 10 mg up to 4 times daily and that an individual variation in need for midodrine is known, the level of the target plasma profile may vary a factor 0.1-5. The shape of the profile is more important than the exact level of plasma concentrations.

- The presumption in making this deconvolution was that the daily dose of midodrine is the same irrespective of whether the new CR composition or a plain tablet or a solution were administered.

25

Presumptions for this estimation are:

- 35 Target release *in vitro* profile estimated as described above:**

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	Time (hours)	% w/w released midodrine
	0.5	25
	1	35
5	2	39
	3	47
	4	53
	5	60
	6	66
10	7	73
	8	80
	9	87
	10	93
	12	100
15		

In order to reflect the second rise in release of midodrine corresponding to the time when the composition reaches the colon, the following target profile is also relevant:

	Time (hours)	% w/w released midodrine
20	0.5	25
	1	35
	2	39
	3	47
	4	53
25	5	60
	6	66
	7	75
	8	90
	9	95
30	10	97
	11	99
	12	100

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As apparent from the above, an initial relatively fast release of midodrine is suitable and after about 6-8 hours a second rise in release should be observed. Accordingly, a target release rate profile is as follow (the release rate is given in % dissolved/hour):

- 5 about 35 %/hour about 30 min after start of the dissolution test,
- about 12 %/hour about 1 hour after start of the dissolution test,
- about 6 %/hour about 2 hours after start of the dissolution test,
- about 7 %/hour about 3 hours after start of the dissolution test,
- about 6.5 %/hour about 4 hours after start of the dissolution test,
- 10 about 6.5 %/hour about 5 hours after start of the dissolution test,
- about 7.5 %/hour about 6 hours after start of the dissolution test,
- about 12 %/hour about 7 hours after start of the dissolution test,
- about 10 %/hour about 8 hours after start of the dissolution test,
- about 3.5 %/hour about 9 hours after start of the dissolution test
- 15 about 2 %/hour about 10 hours after start of the dissolution test,
- about 1 %/hour about 12 hours after start of the dissolution test.

In Fig. 5 is given a target dissolution profile and a target release rate curve.

- 20 As dissolution test any acceptable method may be applied, preferably a method according to USP or Ph.Eur. Throughout the examples 1, 3-10, the following method has been employed: the *in vitro* dissolution method according to USP and Ph.Eur. employing dissolution apparatus 2 (paddle), 100 rpm, 0.1 N hydrochloric acid as dissolution medium and a temperature of 37 °C. It is contemplated that other dissolution media may be
- 25 suitable as well as another rotation speed.

Reference is given to the claims herein where further details concerning the dissolution patterns and the release rates of a controlled release composition of a kit according to the invention are given.

30

With respect to the release of midodrine and/or desglymidodrine from the relatively fast onset composition or part of the kit, the following applies:

Tablets (plain): disintegration time less than 15 min and often less than 5 min such as,

- 35 e.g. 1-3 min.

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Sublingual, buccal and melt tablets: by mould technique: disintegration time less than about 30 sec such as, e.g. about 2-10 sec; by compression or compacting: disintegration time less than about 4 min such as, e.g., about 2-3 min.

- 5 Other compositions normally contain midodrine and/or desglymidodrine in dissolved form. Thus, no retardation of the release of the active drug substance from such compositions is expected.

Specific embodiments of interest are as follows:

10

Controlled release compositions of the kit according the invention, wherein the release pattern of midodrine from the controlled release composition - when tested *in vitro* using Dissolution Method I or II described in the Experimental part herein and employing a basket according to USP and Ph. Eur, 100 rpm, 600 ml 1 N hydrochloric acid as

- 15 dissolution medium and a temperature of 37 °C - is:**

- 1-15% w/w is released from the composition within the first 30 min after start of the test,
10-35% (25%) w/w is released about 30 min after start of the test,
15-40% (35%) w/w is released about 1 hour after start of the test
20 20-50% (39%) w/w is released about 2 hours after start of the test,
20-55% (47%) w/w is released about 3 hours after start of the test,
25-75% such as, e.g., 25-65% (53%) w/w is released about 4 hours after start of the test,
30-74% (66%) w/w is released about 6 hours after start of the test,
40-85% (80%) w/w is released about 8 hours after start of the test,
25 65-100% (93%) w/w is released about 10 hours after start of the test,
90-110% (100%) w/w is released about 12 hours after start of the test.

A release pattern of midodrine from a controlled release composition of the kit according to the invention - when tested *in vitro* using Dissolution Method III or IV described herein and employing a basket according to USP and Ph. Eur, 100 rpm, a first dissolution medium with a pH of about 1.0 for the first 2 hours of the testing followed by a second dissolution medium with a pH of about 6.0 for the next 5.5 hours and finally a third dissolution medium with a pH of about 7.5 until the end of the testing, and a temperature of 37 °C - may also be:

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- 1-15% w/w is released from the composition within the first 30 min after start of the test,
 10-35% (25%) w/w is released about 30 min after start of the test,
 15-40% (35%) w/w is released about 1 hour after start of the test
 20-50% (39%) w/w is released about 2 hours after start of the test,
 5 20-55% (47%) w/w is released about 3 hours after start of the test,
 25-75% such as, e.g., 25-65% (53%) w/w is released about 4 hours after start of the test,
 30-74% (66%) w/w is released about 6 hours after start of the test,
 40-95% such as, e.g., 45-85% (80%) w/w is released about 8 hours after start of the test,
 65-100% (93%) w/w is released about 10 hours after start of the test,
 10 75-110% (100%) w/w is released about 12 hours after start of the test.

Another release pattern of midodrine from a controlled release composition of a kit according to the present invention - when tested *in vitro* employing any of Dissolution Method I, II, III or IV as described herein, - is as follows ($\pm 30\%$ w/w such as, e.g., $\pm 25\%$,

- 15 $\pm 20\%$, $\pm 15\%$ or $\pm 10\%$ of the values stated below):

- about 25% w/w is released about 30 min after start of the test,
 about 35% w/w is released about 1 hour after start of the test,
 about 39% w/w is released about 2 hours after start of the test,
 20 about 47% w/w is released about 3 hours after start of the test,
 about 53-56% such as, e.g., about 53% w/w is released about 4 hours after start of the test,
 about 66-72% such as, e.g., about 66% w/w is released about 6 hours after start of the test,
 25 about 80-85% w/w is released about 8 hours after start of the test,
 about 93% w/w is released about 10 hours after start of the test,
 about 100% w/w is released about 12 hours after start of the test.

- A still further release pattern of midodrine from a controlled release composition of a kit according to the invention - when tested *in vitro* employing any of Dissolution Method I, II, III or IV as described herein - is:
- 30

- 1-15% w/w is released from the composition within the first 30 min after start of the test,
 10-35% (25%) w/w is released about 30 min after start of the test,
 35 15-40% (35%) w/w is released about 1 hour after start of the test,

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- 20-50% (39%) w/w is released about 2 hours after start of the test,
 20-55% (47%) w/w is released about 3 hours after start of the test,
 25-75% such as 25-65% (53%) w/w is released about 4 hours after start of the test,
 30-74% (66%) w/w is released about 6 hours after start of the test,
 5 35-85% (75%) w/w is released about 7 hours after start of the test,
 45-95% (90%) w/w is released about 8 hours after start of the test,
 65-100% (97%) w/w is released about 10 hours after start of the test,
 90-110% (100%) w/w is released about 12 hours after start of the test.
- 10 Another suitable release pattern of midodrine from a controlled release composition of a kit according to the invention - when tested *in vitro* employing any of Dissolution Method I, II, III or IV as described herein - is:
- 1-15% w/w is released from the composition within the first 30 min after start of the test,
 15 15-35% (25%) w/w is released about 30 min after start of the test,
 20-40% (35%) w/w is released about 1 hour after start of the test,
 25-50% (39%) w/w is released about 2 hours after start of the test,
 30-55% (47%) w/w is released about 3 hours after start of the test,
 40-75% such as, e.g., 40-65% (53%) w/w is released about 4 hours after start of the test,
 20 50-74% (66%) w/w is released about 6 hours after start of the test,
 60-85% (75%) w/w is released about 7 hours after start of the test,
 70-95% (90%) w/w is released about 8 hours after start of the test,
 80-100% (97%) w/w is released about 10 hours after start of the test,
 90-110% (100%) w/w is released about 12 hours after start of the test.
- 25 In other aspects, the release pattern of midodrine from a controlled release composition of a kit according to the invention - when tested *in vitro* employing any of Dissolution Method I, II, III or IV as described herein - is as follows ($\pm 30\%$ w/w, $\pm 20\%$ w/w, $\pm 10\%$ w/w, $\pm 7.5\%$ w/w or $\pm 5\%$ w/w of the values stated below):
- 30 about 25% w/w is released about 30 min after start of the test,
 about 35% w/w is released about 1 hour after start of the test,
 about 39% w/w is released about 2 hours after start of the test,
 about 47% w/w is released about 3 hours after start of the test,
 35 about 53% w/w is released about 4 hours after start of the test,

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25 below):

about 20% w/w is released about 30 min after start of the test,
about 20% w/w is released about 1 hour after start of the test,
about 20% w/w is released about 2 hours after start of the test,
about 20% w/w is released about 3 hours after start of the test,
30 about 25% w/w is released about 4 hours after start of the test,
about 45 w/w is released about 6 hours after start of the test,
about 75% w/w is released about 7 hours after start of the test,
about 90% w/w is released about 8 hours after start of the test,
about 95% w/w is released about 10 hours after start of the test,
35 about 100% w/w is released about 12 hours after start of the test.

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10 midodrine.

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medium or any of Dissolution Method I, II, III or IV as described herein and a temperature

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of 37 °C - in %/hour is as follows ($\pm 10-40\%$ such as, e.g. $\pm 10-30\%$ or $\pm 10\%$, $\pm 15\%$ or $\pm 20\%$ of the values stated below):

- about 35 %/hour about 30 min after start of the test (range e.g. 15-40 %/hour),
 - 5 about 12 %/hour about 1 hour after start of the test (range e.g. 4-15 %/hour),
 - about 6 %/hour about 2 hours after start of the test (range e.g. 2-10 %/hour),
 - about 7 %/hour about 3 hours after start of the test (range e.g. 2-10 %/hour),
 - about 6.5 %/hour about 4 hours after start of the test (range e.g. 2-15 %/hour),
 - about 7.5 %/hour about 6 hours after start of the test (range e.g. 2-30% such as, e.g., 2-
 - 10 10 %/hour),
 - about 10 %/hour about 8 hours after start of the test (range e.g. 2-15 %/hour),
 - about 2 %/hour about 10 hours after start of the test (range e.g. 0-10 %/hour),
 - about 1 %/hour about 12 hours after start of the test (range e.g. 0-10 %/hour).
- 15 A controlled release composition of a kit according to the invention is normally suitable for administration once or twice daily, and it differs from a plain tablet composition, e.g. Gutron® tablets, in many ways. In the following is given pharmacokinetic values of importance for achievement of a prolonged therapeutic effect of a composition according to the invention. Further details concerning the definition of the parameters and the
- 20 method of obtaining relevant values are given in Example 15 herein.

When tested as described in Example 15 herein, W_{50} of midodrine (defined as corresponding to the time the plasma concentration curve is or is above 50% of the C_{max} value) is from about 1 to about 9 hours such as, e.g. from about 1.3 to about 8 hours such

25 as, e.g. at least about 1.4 hours, at least about 1.5 hours, or at least about 1.7 hours.

Compared with a standard midodrine composition, W_{50} is increased with a factor of at least 2 such as, e.g., at least 2.5. A suitable comparison is performed against a plain Gutron® tablet administered in the same dose and W_{50} is determined from a plasma

30 concentration versus time curve. The plasma concentration reflects the sum concentration in nmol/l of midodrine and desglymidodrine.

Analogously, W_{75} ($T > 75\% C_{max}$) is increased with a factor of at least 2 when compared with a plain Gutron® tablet administered in the same dose. W_{75} ($T > 75\% C_{max}$) is

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determined from a plasma concentration versus time curve and the plasma concentration reflects the sum concentration in nmol/l of midodrine and desglymidodrine .

- Likewise, W_{50} of desglymidodrine (defined as corresponding to the time the plasma concentration curve is or is above 50% of the C_{max} value) is from about 5 to about 12 hours such as, e.g. from about 6 to about 11 hours such as, e.g. at least about 7 hours.

- Furthermore, T_{max} is increased with a factor of at least 2 when compared with a plain Gutron® tablet administered in the same dose. T_{max} is determined from a plasma concentration versus time curve and the plasma concentration reflects the sum concentration in nmol/l of midodrine and desglymidodrine.

- MRT (mean residence time) is increased with a factor of at least 1.5 such as, e.g., at least 2, at least 2.5 or at least 3 when compared with a plain Gutron® tablet administered in the same dose. MRT is determined from a plasma concentration versus time curve and the plasma concentration reflects the sum concentration in nmol/l of midodrine and desglymidodrine.

- MRT for midodrine is at least about 1.5 hours such as, e.g., at least about 2 hours, at least about 2.5 hours or at least about 3 hours, and/or MRT for desglymidodrine is at least about 6 hours such as, e.g., at least about 7 hours, at least about 7.5 hours, at least about 8 hours, at least about 8.5 hours, at least about 9 hours, or at least about 9.5 hours.

Active drug substances

- As mentioned above, a kit according to the invention is suitable for use for any active drug substance for which a dissolution pattern as described above is of relevance, and which beneficially can be administered only once or twice daily.
- With respect to treatment of orthostatic hypotension and the other conditions mentioned above, midodrine and its active metabolite desglymidodrine are drugs of choice.

Midodrine as well as desglymidodrine exist in racemic form and in the form of the two enantiomeric species.

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Desglymidodrine is also known as ST 1059, alpha-(aminomethyl)-2,5-dimethoxy-benzenemethanol. It may be present in racemic form, i.e. as (±)-desglymidodrine, (±)-ST1059 or (±)-alpha-(aminomethyl)-2,5-dimethoxy-benzenemethanol, or in its enantiomeric form as (-)-desglymidodrine, (R)-desglymidodrine, (-)-ST1059, (R)-ST1059, (-)-alpha-(aminomethyl)-2,5-dimethoxy-benzenemethanol or (R)-alpha-(aminomethyl)-2,5-dimethoxy-benzenemethanol, or in its other enantiomeric form (+)-desglymidodrine, (S)-desglymidodrine, (+)-ST1059, (S)-ST1059, (+)-alpha-(aminomethyl)-2,5-dimethoxy-benzenemethanol or (S)-alpha-(aminomethyl)-2,5-dimethoxy-benzenemethanol.

A composition of a kit according to the invention may therefore include midodrine in the racemic form (RS), in the enantiomeric form (R), in the enantiomeric form (S) or in mixtures thereof.

25 In an embodiment according to the invention the kit comprises a composition which includes at least 90% w/w such as, e.g., at least 95% w/w, at least 97% w/w, at least 98% w/w, at least 99% w/w of midodrine in the therapeutically active enantiomeric form; and the therapeutically active enantiomeric form of midodrine is (-)-2-amino-N-(β -hydroxy-2,5-

30 dimethoxyphenethyl)-acetamide or the (R) form of midodrine.

In another embodiment according to the invention, a composition contains the active metabolite desglymidodrine (ST 1059), and desglymidodrine is present in the form of (±)-α-(aminomethyl)-2,5-dimethoxy-benzenemethanol (± ST 1059), (+)-α-(aminomethyl)-2,5-

In a still further embodiment a composition of a kit according to the invention contains desglymidodrine in the racemic form (RS), in the enantiomeric form (R), in the enantiomeric form (S) or in mixtures thereof, or it contains at least 90% w/w such as, e.g., at least 95% w/w, at least 97% w/w, at least 98% w/w, at least 99% w/w of desglymidodrine is present in the therapeutically active enantiomeric form. The therapeutically active enantiomeric form of desglymidodrine is contemplated to be (-)- α -(aminomethyl)-2,5-dimethoxy-benzenemethanol (- ST 1059) or the (R) form of desglymidodrine ((R) ST 1059).

In a composition according to the invention midodrine and/or desglymidodrine are present in the form of a pharmaceutically acceptable salt such as a salt formed between midodrine and/or desglymidodrine and an inorganic acid such as e.g., a hydrochloride, a hydrobromide, a hydroiodide, a nitrate, a nitrite, a H_3PO_3 salt, a H_3PO_4 salt, a H_2SO_3 salt, a sulfate, a H_2SO_6 salt, or a salt formed between midodrine and/or desglymidodrine and an organic acid such as organic acids like e.g. H_2CO_3 , acetic acid, $\text{C}_2\text{H}_5\text{COOH}$, $\text{C}_3\text{H}_7\text{COOH}$, $\text{C}_4\text{H}_9\text{COOH}$, $(\text{COOH})_2$, $\text{CH}_2(\text{COOH})_2$, $\text{C}_2\text{H}_6(\text{COOH})_2$, $\text{C}_3\text{H}_8(\text{COOH})_2$, $\text{C}_4\text{H}_8(\text{COOH})_2$, $\text{C}_5\text{H}_{10}(\text{COOH})_2$, fumaric acid, maleic acid, lactic acid, tartaric acid, citric acid, ascorbic acid, benzoic acid, salicylic acid and phthalic acid

A composition according to the invention may comprise a further active drug substance, i.e. the composition may be in the form of a so-called combination composition comprising at least two different active drug substances. The further active drug substance may be any active drug substance, which beneficially is used in combination with midodrine and/or desglymidodrine. Interesting examples of further active drug substances are steroids like e.g. hydrocortisone or fludrocortisone or somatostatin analogues like e.g. octreotide.

Dosage

In general, the dosage of the active drug substance present in a composition according to the invention depends *inter alia* on the specific drug substance, the age and condition of the patient and of the disease to be treated.

With respect to midodrine, the normal daily dose is from 2.5 to 10 mg three or up to four times daily (calculated as midodrine hydrochloride), i.e. a daily dose of from about 7.5 mg to about 40 mg in the treatment of orthostatic hypertension. However, the daily dose in the treatment of urinary incontinence may be different and, accordingly, a composition according to the present invention typically contains from about 2.5mg to about 50 mg midodrine such as, e.g. 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg or 50 mg. In the cases, where midodrine is employed in another form, e.g. in another salt form than midodrine hydrochloride, the above-mentioned dosage ranges are of course to be recalculated so that the same dosage is employed on a molar basis.

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5 The individual fast onset doses of the kit of the invention may be from 0.2 mg to 10 mg, preferably from 0.5 mg to 7.5 mg such as of 0.75 mg, 1 mg, 1.25 mg, 1.5 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, or 5 mg.

With respect to the dosage in those cases where desglymidodrine is employed it is
15 envisaged that the same dosages as mentioned above are relevant.

In principle any relevant controlled formulation technique for preparing an oral controlled release composition may be applied. Thus, the dosage form may be in the form of a liquid having e.g. particles dispersed in a dispersion medium or it may be in the form of a single or a multiple unit dosage form intended for use as such as for dispersing in a dispersion medium before use.

25 Any relevant formulation technique for preparing pharmaceutical compositions may be applied when formulating the relatively fast onset composition. A person skilled in the art of pharmaceutical formulation techniques can find guidance in the handbook Remington's Pharmaceutical Sciences and in the Examples herein.

30 In the following is given a short review on general controlled release formulation techniques with an aim of obtaining the type of dissolution profile described above. In the compositions described below a person skilled in the art will know how to incorporate a part that gives rise to a relatively fast release of the active drug substance. As an example, such a part may be incorporated in an outermost coating layer comprising the

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active substance or it may be incorporated in the form of pellets formulated without
retarding agents neither in the cores nor in a coating.

Examples of different controlled release technologies are:

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1. Single units

1.1 Coated matrix

1.2 Double or triple compression

1.3 Multilayer coating

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2. Multiple units

2.1 Units having a controlled release coating

2.2 Units having a controlled release matrix

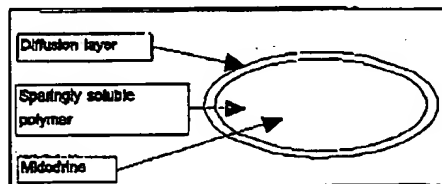
2.3 Units having a controlled release compression coating

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2.4 Units with a multilayer coating.

Coated matrix

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The idea behind the use of this technology is to coat a sparingly soluble and/or swellable polymer, in which midodrine (and/or any relevant substance such as, e.g. desglylmidodrine) is embedded, with an insoluble diffusion barrier. The diffusion of midodrine is controlled by the matrix and the coat. This technique will cover the type of dissolution profile described in
step 2 above.

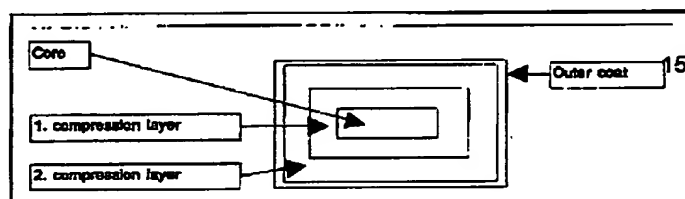
If a soluble outer film layer containing midodrine is applied on the coated matrix, step 1 is achievable too.

Step 3 can be covered by including enteric coated units embedded in the matrix.

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Double or Triple compression

- The basic idea for such a formulation is a core of a polymer having midodrine and/or desglymidodrine incorporated. This core is compression coated with a polymer with midodrine incorporated in the same or another concentration than in the core. When triple compression is employed, the coated core is compression coated once more with a polymer with midodrine in the same or another concentration as in the first coat. Finally, the double or triple compression unit is spray coated and midodrine is incorporated in the coat.
- However, the concentrations of midodrine in the different coats may vary markedly. The idea behind the multiple layers is that when the midodrine of the first layer has been almost depleted, the next layer takes over and levels out or changes the release profile.



- The spray coating with midodrine and/or desglymidodrine gives an immediate burst of the active compound.

Steps 1, 2 and 3 can be covered by use of this technique.

25 Multilayer coating

The idea with this type of formulation is to coat an inert core with several layers of diffusion barriers, each barrier containing different concentrations of midodrine. The concentration should be highest in the inner coat and lowest in the outer coat.

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The purpose of the concentration gradient is to compensate for the increasing diffusion distance closer to the core. If the thickness of the diffusion barriers and the concentration gradients are correctly adjusted, steps 1, 2 and 3 will be obtainable.

35 Use of enteric coating

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5 Use of amylose as colon degradable excipient

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Multiple unit systems

The units comprise pellets, granules, crystals, mini tablets or mixtures thereof.

15 Step 1 can be covered by an uncoated unit.

Step 2 can be covered by the application of a controlled release coating or by formulating the unit as a matrix or a coated matrix.

20 Step 3 can be covered by the use of an enteric polymer or amylose, or by having units compressed as described in the triple compression technology.

In specific embodiments, a composition of a kit according to the invention is in the form of a solid dosage form such as, e.g., tablets, capsules, sachets, solid dispersion, crystals, granules and the like.

A controlled release composition of a kit according to the invention can also comprise at least two parts such as at least a first and a second part, each part contains midodrine and/or, if present, desglylmidodrine and the first part being adapted to release midodrine and/or, if present, desglylmidodrine, in a controlled manner during the first 0-14 such as, e.g. 0-11 hours after oral intake and the second part being adapted to release midodrine and/or, if present, desglylmidodrine, starting at least 6 hours after oral intake.

In such a composition at least one of the at least two parts is present in the composition in the form of a multiplicity of individual units such as, e.g. pellets or minitabets.

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The two parts of the at least two parts may also be present in the composition in the form of a multiplicity of individual units such as, e.g. pellets or minitabets, and the two parts may be in admixture.

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A controlled release composition of a kit according to the invention may also be in multiple unit dosage form such as, e.g., wherein at least one of the at least two parts comprises at least two different types of pellets, the first type of pellets corresponding to a first fraction and the second type of pellets corresponding to a second fraction.

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Moreover, the at least two parts of the controlled release composition may comprise at least two different types of pellets, the first type of pellets corresponding to the first part and the second type of pellets corresponding to the second part.

- 15 A controlled release composition of a kit according to the invention may also as individual units contain minitabets, i.e. be in the form of a multiple unit dosage form comprising at least two different types of minitabets, the first type of minitabets corresponding to the first part and the second type of minitabets corresponding to the second part. In the present context a minitabets is a tablet having a size in a range corresponding to from
- 20 about 0.7 mm to about 7 mm in diameter such as, e.g., in a range corresponding to from about 1 to about 7 mm, from about 1.5 to about 6 mm, from about 2 mm to about 5 mm, from about 2 mm to about 4 mm such as in a range corresponding to from about 2 to about 3 mm in diameter.

- 25 A controlled release composition of a kit according to the invention may also as individual units contain relatively large crystals of the active drug substance. In such cases, the size of the unit is at the most about 1 mm such as, e.g., in a range corresponding to from about 0.1 to about 1 mm, from about 0.2 mm to about 0.8 mm, from about 0.2 mm to about 0.7 mm or from about 0.3 mm to about 0.7 mm.

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A controlled release composition of a kit according to the invention may be in the form of a multiple unit dosage form, wherein the first or the second part is in the form of minitabets, in the form of pellets or in the form of large crystals of the active drug substance.

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Furthermore, a composition of a kit according to the invention may comprise a third part adapted to release midodrine and, if present, desglymidodrine relatively fast from the composition and/or a fourth part adapted to release midodrine and/or desglymidodrine from the composition 6-10 hours after oral intake.

In one embodiment the third and/or, if present, the fourth part comprise pellets or

With respect to release kinetics, a controlled release composition of a kit according to the invention may have a first part, a second part, a third part and/or a fourth part which have a release kinetic corresponding to a zero or a first order release or a mixture of zero and

All the above-mentioned combinations of different types of compositions or formulation techniques apply, whenever relevant, mutatis mutandi to the fast release part or composition of the kit of the invention. The same applies to the combination of the controlled release part or composition and the fast release part or composition of a kit of the invention

25 Apart from the active drug substance in the composition, a pharmaceutical composition according to the invention may further comprise pharmaceutically acceptable excipients.

In the present context, the term "pharmaceutically acceptable excipient" is intended to denote any material, which is inert in the sense that it substantially does not have any therapeutic and/or prophylactic effect *per se*. A pharmaceutically acceptable excipient may be added to the active drug substance with the purpose of making it possible to obtain a pharmaceutical composition, which has acceptable technical properties.

Fillers/diluents/binders may be incorporated such as sucrose, sorbitol, mannitol, lactose (e.g., spray-dried lactose, α -lactose, β -lactose, Tabletose®, various grades of Pharma-

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5 LH 20, LH 32, LH 31, LH30), dextrins, maltodextrins (e.g. Lodex® 5 and Lodex® 10), starches or modified starches (including potato starch, maize starch and rice starch), sodium chloride, sodium phosphate, calcium phosphate (e.g. basic calcium phosphate, calcium hydrogen phosphate), calcium sulfate, calcium carbonate, gelatine, polyvinylpyrrolidone (30, 90, Kollidon VA 64), and sodium carboxymethylcellulose.

Disintegrants may be used such as cellulose derivatives, including microcrystalline cellulose, low-substituted hydroxypropyl cellulose (e.g. LH 11, LH 22, LH 21, LH 20, LH 32, LH 31, LH30); starches, including potato starch; croscarmellose sodium (i.e. cross-linked carboxymethylcellulose sodium salt; e.g. Ac-Di-Sol®); alginic acid or alginates; insoluble

20 Glidants and lubricants may be incorporated such as stearic acid, metallic stearates, talc, waxes and glycerides with high melting temperatures, colloidal silica, sodium stearyl fumarate, polyethyleneglycols and alkyl sulphates.

Surfactants may be employed such as non-ionic (e.g., polysorbate 20, polysorbate 21, polysorbate 40, polysorbate 60, polysorbate 61, polysorbate 65, polysorbate 80, polysorbate 81, polysorbate 85, polysorbate 120, sorbitane monoisostearate, sorbitanmonolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan monooleate, sorbitan sesquioleate, sorbitan trioleate, glyceryl monooleate and polyvinylalcohol), anionic (e.g., docusate sodium and sodium lauryl sulphate) and cationic (e.g., benzalkonium chloride, benzethonium chloride and cetrimide) or mixtures thereof.

Examples of amphoteric surfactants are 1,2-diacyl-L-phosphatidylcholine, N-lauryl-N,N-dimethylglycine, alkylaminopropionic acid, alkyliminodipropionic acid, and dimethyl-(3-palmitamidopropyl)-aminoacetate.

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5 Modified release coating

10 The modified release coating is a substantially water-insoluble but water-diffusible coating.

15 coating composition may also be applied. The modified release coating may also be applied as a compression coating comprising a dry mixture of polymer(s) and the e.g. the active drug substance.

Examples of matrix-forming agents are hydroxypropylmethylcellulose such as, e.g., 1828, 2208, 2906 or 2910 according to USP, hydroxypropylcellulose, micronised ethylcellulose, low-substituted hydroxypropylcellulose (LH 20, 21, 31).

Examples of film-forming agents which are suitable for use in accordance with the present invention are agents selected from the group consisting of cellulose derivatives such as, 25 e.g., ethylcellulose, cellulose acetate, cellulose propionate, cellulose butyrate, cellulose valerate, cellulose acetate propionate; acrylic polymers such as, e.g., polymethyl methacrylate; vinyl polymers such as, e.g., polyvinyl acetate, polyvinyl formal, polyvinyl butyryl, vinyl chloride-vinyl acetate copolymer, ethylene-vinyl acetate copolymer, vinyl chloride-propylene-vinyl acetate copolymer; silicon polymers such as, e.g., ladder polymer 30 of sesquiphenyl siloxane, and colloidal silica; polycarbonate; polystyrene; polyester; coumarone-indene polymer; polybutadiene; and other high molecular synthetic polymers.

In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in

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The amount of coating applied is adapted so as to obtain a predetermined dissolution characteristic of the composition.

The coating may be admixed with various excipients such as plasticizers, anti-adhesives such as, e.g., colloidal silicium dioxide, inert fillers, lipophilic agents such as, e.g., stearic

[illegible]

5 incorporating an anti-adhesive in the coating. The anti-adhesive is preferably a finely divided, substantially insoluble, pharmaceutically acceptable non-wetting powder having anti-adhesive properties in the coating. Examples of anti-adhesives are metallic stearates such as magnesium stearate or calcium stearate, microcrystalline cellulose, or mineral substances such as calcite, substantially water-insoluble calcium phosphates or substantially water-insoluble calcium sulphates, colloidal silica, titanium dioxide, barium sulphates, hydrogenated aluminium silicates, hydrous aluminium potassium silicates and talc. The preferred anti-adhesive is talc. The anti-adhesive or mixture of anti-adhesives is preferably incorporated in the coating in an amount of about 0.1-70% by weight, in particular about 1-60% by weight, and preferably about 8-50% by weight of the film layer.

15 By selecting a small particle size of the talc, a larger surface area is obtained; the consequent higher anti-adhesive effect makes it possible to incorporate smaller amounts of specific anti-adhesives.

20

In one aspect, the outer second layer comprises a water-based film-forming agent which prevents adhesion between the units at elevated temperatures and imparts flowability to the units, the water-based film-forming agent being anti-adhesive at temperatures above about 40 °C, especially temperatures above about 50 °C, such as a temperature between about 60 °C and about 120 °C, and being selected from diffusion coating materials such as ethylcellulose or enteric coating materials such as anionic poly(meth)acrylic acid esters, hydroxypropylmethylcellulosephthalate, celluloseacetatephthalate, polyvinylacetatephthalate, polyvinylacetatephthalate-crotonic acid copolymerisates, or mixtures thereof, or water-soluble coating materials such as water-soluble cellulose derivatives, e.g. hydroxypropylcellulose, carboxymethylcellulose, methylcellulose, propylcellulose, hydroxyethylcellulose, carboxyethylcellulose, carboxymethylhydroxyethylcellulose, hydroxymethylcellulose, carboxymethylethylcellulose, methylhydroxypropylcellulose or hydroxypropylmethylcellulose.

Examples of plasticizers for use in accordance with the present invention include triacetin, acetylated monoglyceride, rape oil, olive oil, sesame oil, acetyl tributyl citrate, acetyl triethyl citrate, glycerin, sorbitol, diethyloxalate, diethylmalate, diethylmaleate, diethylfumarate, diethylsuccinate, diethylmalonate, dioctylphthalate, dibutylsebacate, triethylcitrate, tributylcitrate, glyceroltributyrate, polyethyleneglycol, propyleneglycol, 1,2-propyleneglycol, dibutylsebacate, diethylsebacate and mixtures thereof. The plasticizer is normally incorporated in an amount of less than 20% by weight, calculated on the dry matter content of the coating composition.

10 The fast onset composition of a kit according to the invention may be any composition well known in the art to provide a relative fast release.

With respect to nasal vehicles, polyethyleneglycols is especially preferred such as more n-ethylene glycols represented by the following formula

15



wherein p is an integer in the range of 1 to 14. Examples of n-ethylene glycols are monoethylene glycol (1EG), diethylene glycol (2EG), triethylene glycol (3EG),

20 tetraethylene glycol (4EG), pentaethylene glycol (5EG), hexaethylene glycol (6EG), heptaethylene glycol (7EG), octaethylene glycol (8EG), nonaethylene glycol (9EG), decaethylene glycol (10EG), undecaethylene glycol (11EG), dodecaethylene glycol (12EG), tridecaethylene glycol (13EG), and tetradecaethylene glycol (14EG). The ethylene glycols may be used in the form of the single compounds or as a mixture of two

25 or more n-ethylene glycols, e.g. commercial products such as polyethylene glycol 200 (PEG 200), polyethylene glycol 300 (PEG 300) or polyethylene glycol 400 (PEG 400). The polyethyleneglycols may be used in combination with glycofurols (α -[tetrahydro-2-furanyl)methyl]- ω -hydroxy-poly(oxy-1,2-ethanediyl)). The latter may also be used separately.

30

The volume of a nasal dosage is preferably within 500 μ l such as within 300 μ l such as in a range of 10-250 μ l.

The invention is further illustrated in the drawing, wherein

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- fig. 1 shows the estimated plasma concentration of midodrine ,
 fig. 2 shows the estimated plasma concentration of desglymidodrine,
 fig. 3 shows the estimated *in vivo* dissolution of midodrine,
 fig. 4 shows the estimated *in vivo* dissolution of desglymidodrine,
 5 fig. 5 shows the estimated *in vitro* target for dissolution of midodrine and the estimated release rate,
 figs. 6-9 illustrate the results of Example 1,
 figs. 10-13 illustrate the results of Example 3,
 figs. 14-16 illustrate the results of Example 4,
 10 figs. 17-18 illustrate the results of Example 2,
 figs. 19 and 20 the results of Example 12,
 fig. 21 illustrates the results of Example 13,
 fig. 23 illustrates the results of Example 14, and
 figs. 23-24 illustrate the results of Example 15.

15

The following examples are intended to illustrate specific embodiments of the present invention but are not intended in any way to limit the invention. Some of the examples are included in order to illustrate that the release rate and dissolution characteristics of a composition can be changed by varying a number of formulation parameters.

20

METHODS

DISSOLUTION METHOD I FOR MITAB (midodrine hydrochloride triple compression tablets).

25

Apparatus	Ph.Eur /USP dissolution apparatus + Perkin Elmer fully automatic dissolution system + Disslab PC-programme
Glass fibre filter	0.7 µm
Dissolution medium	600 ml 0.1N HCl
Rotation speed	100 rpm
Stirrer	Basket
Sampling times	As appear from tables
Detection wavelength	290 nm
Measuring equipment	UV-spectrophotometer, 10 mm quartz cuvette

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Temperature of dissolution medium $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ Reagents:

0.1N HCl is prepared by dilution of concentrated HCl (37%) with purified water.

5 Standards:

Two solutions are prepared with a concentration of 10 µg/ml midodrine hydrochloride in 0.1 N HCl. 0.1 N HCl is used as blind. The absorbances of the solutions are measured on the spectrophotometer.

 $E_{1\%/\text{cm}}$ is calculated.

- 10 $E_{1\%/\text{cm}} = A \times 1000$, where 1000 is due to the fact, that the solution is only 0.001%. The mean value of the 10 measurements is inserted in the software programme in accordance with the manual for the automated dissolution system.

Performance:

- 15 600 ml 0.1N HCl is filled in each of the six vessels in the dissolution equipment. The media is heated to a temperature of $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. One weighed tablet is placed in each of the six baskets. The stirring is started as soon as the baskets are lowered into the vessels. The sample is filtered through a 0.7 µm filter. The absorbances of the filtered samples are measured directly at 290 nm.

20

DISSOLUTION METHOD II FOR MITAB (midodrine hydrochloride triple compression tablets). HPLC-detection.

The dissolution parameters are described in Method I. The measurement is performed by

25 HPLC.

Column	Spherisorb ODS-1; 5 µm; 25 cm; ID 4.6 µm
Injection volume	20 µl
Flowrate	1.0 ml/min
Mobile phase	Phosphate buffer pH 3: methanol 77:23 (v/v)
Detection	290 nm
Runtime	30 min

Reagents for dissolution are described in Method I.

Buffer solution pH 3 is prepared by dissolving 23.6 g potassium dihydrogen phosphate in 900 ml purified water. o-Phosphoric acid 85% is used to adjust pH. The flask is filled to 1 l.

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Standards:

Two stock solutions with a concentration of midodrine hydrochloride 120 µg/ml in 0.01 N HCl are prepared. The solutions are stored in refrigerator.

- 5 Prepare from each stock solution two standard solutions with a concentration of midodrine hydrochloride approximately 1.5 µg/ml and 15 µg/ml respectively, diluted with 0.01N HCl. Desglymidodrine hydrochloride is quantified against the standard curve of midodrine hydrochloride. The relative response factor is 1.25 for Desglymidodrine hydrochloride to midodrine hydrochloride.

10

Performance:

The dissolution is performed as described in Method I. The sample is withdrawn with a pipette and transferred to a syringe. The sample is filtered through a 0.7 µm filter. The first ml is returned to the vessel in order to reduce deviation from the desired volume. A

- 15 sample of approximately 1.5 - 2 ml is transferred to the vial, the rest is returned to the vessel. The absorbances of the filtered samples are measured as described.

Calculations:

A standard curve is calculated by linear regression, using the standard solutions. The

- 20 peak area of the sample is the sum of the peak area of Midodrine Hydrochloride and the peak area of Desglymidodrine hydrochloride, where the latter is divided by the relative response factor 1.25.

The results are calculated as % released at any time and presented as a mean value of the six samples together with min and max.

$$\% \text{ dissolved} = \frac{A \text{ vol } 100}{b \times}$$

25

Where

A sum of peak area of midodrine hydrochloride and Desglymidodrine hydrochloride (corr.)

- 30 Vol 600 ml for tablets (MITAB)

100 %

b slope of the calibration curve (A/mg/ml)

x declared amount (mg)

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DISSOLUTION METHOD III FOR MICAP (midodrine hydrochloride multiple unit**5 capsules).**

Apparatus	Ph.Eur /USP dissolution apparatus + Perkin Elmer fully automatic dissolution system + Disslab PC-programme
Glass fibre filter	0.7 μ m
Dissolution medium at the beginning	600 ml 0.1N HCl
Dissolution media at change to pH 6.0	Addition of 130 ml 0.23 M Na_3PO_4 solution
Dissolution media at change to pH 7.5	Addition of further 70 ml 0.23 M Na_3PO_4 solution
Time for change to pH 6.0	2 hours (120 min)
Time for change to pH 7.5	7.5 hours (450 min)
Rotation speed	100 rpm
Stirrer	Basket
Sampling times	As appear from tables
Detection wavelength	290 nm
Measuring equipment	UV-spectrophotometer, 10 mm quartz cuvette
Temperature of dissolution medium	37°C \pm 0.5°C
Reference (vessel no 7)	An empty capsule dissolved in 600 ml 0.1N HCl
Vessel no 7 is added Na_3PO_4 solution in parallel with the six sample vessels	

Reagents:

0.1 N HCl is prepared by dilution of concentrated HCl (37%) with purified water.

- 10 0.23 M Na_3PO_4 solution: Dissolve an amount of $\text{Na}_3\text{PO}_4 \cdot 12\text{H}_2\text{O}$ in a bit of 1M HCl-R and add water to a concentration of 0.23 M. (Strong alkaline).

Buffer solution pH 6.0: 600 ml 0.1 N HCl is added 130 ml 0.23 M Na_3PO_4 solution.

Buffer solution pH 7.5: Buffer solution pH 6.0 is added further 70 ml 0.23 M Na_3PO_4 solution.

15

Standards:

Two solutions are prepared with a concentration of 10 $\mu\text{g/ml}$ midodrine hydrochloride in 0.1 N HCl. 0.1N HCl is used as blind. The absorbances of the solutions are measured on the spectrophotometer.

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The mean value of the n measurements is inserted in the software programme in

5 accordance with the manual for the automated dissolution system.

600 ml 0.1N HCl is filled in each of the seven vessels in the dissolution equipment. The media is heated to a temperature of $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. One weighed capsule is placed in each of the six baskets. In the seventh basket an empty capsule is placed. This is measured as a blank reference. The stirring is started as soon as the baskets are lowered into the vessels. The measured amounts of buffer solution, needed for the changes of pH in the vessels, are preheated to 37°C , before addition to the vessels. When the buffer is to be added, the baskets are elevated from the vessels, the buffer is added, the solution in the vessel is stirred to homogenise the solution and the baskets are lowered into the vessels again. The sample is filtered through a $0.7\ \mu\text{m}$ filter. The absorbances of the filtered samples are measured directly at 290 nm.

20 DISSOLUTION METHOD IV FOR MICAP (midodrine hydrochloride multiple unit capsules), HPLC-detection.

The dissolution parameters are described in Method III. The measurement is performed by HPLC.

Column	Spherisorb ODS-1; 5 µm; 25 cm; ID 4.6 µm
Injection volume	20 µl
Flowrate	1.0 ml/min
Mobile phase	Phosphate buffer pH 3; methanol 77:23 (v/v)
Detection	290 nm
Runtime	30 min

25

Reagents for dissolution are described in Method III.

Buffer solution pH 3 is prepared by dissolving 23.6 g potassium dihydrogen phosphate in 900 ml purified water. o-Phosphoric acid 85% is used to adjust pH. The flask is filled to 1 l.

30 Standards:

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Prepare from each stock solution two standard solutions with a concentration of midodrine hydrochloride approximately 1.5 µg/ml and 15 µg/ml respectively, diluted with 0.01N HCl.

- Performance:**

- 15

A standard curve is calculated by linear regression, using the standard solutions. The peak area of the sample is the sum of the peak area of midodrine hydrochloride and the peak area of desglymidodrine hydrochloride, where the latter is divided by the relative

- The results are calculated as % released at any time and presented as a mean value of the six samples together with min and max.

$$\% \text{ dissolved} = \frac{A \text{ vol } 100}{b \times}$$

- A** sum of peak area of midodrine hydrochloride and desglymidodrine hydrochloride
(corr.)

- Vol** 600 ml for up to 2 hours 730 ml for up to 7.5 hours and 800 ml for up to 12 hours
for capsules (MICAP)

- b** slope of the calibration curve (A/mg/ml)

- x declared amount (mg)

DISSOLUTION METHOD V. Dissolution method used for Midodrine Melt Tablets

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Dissolution apparatus 2 according to USP and Ph. Eur.

Paddle method

Rotations: 50 rpm

5 Temperature: 37°C

Dissolution medium: isotonic buffer pH 6.8 or purified water

Volumen: 600 ml

Sample time: 5 min

RP-HPLC: Phosphate buffer pH 3 : methanol 77:23 (v/v)

10 Detection at 290 nm.

DISSOLUTION METHOD VI for Midodrine Sublingual Tablets

Dissolution apparatus 2 according to USP and Ph. Eur.

15 Paddle method

Rotations: 50 rpm

Temperature: 37°C

Dissolution medium: isotonic buffer pH 6.8 or purified water

Volume: 600 ml

20 Sampling time: 5 min

RP-HPLC: Phosphate buffer pH 3 : methanol 77:23 (v/v)

Detection at 290 nm.

EXAMPLES

25

Example 1**Composition made by employment of triple compression**

30 A tablet was prepared from the following ingredients:

Core:

35	Midodrine hydrochloride	5.0 mg
	Klucel MF	2.0 mg

44

93.0 mg

5

1.5 mg

6.6 mg

156.9 mg

10

2.8 mg

247.2 mg

The following results were obtained with respect to dissolution and release rate (the dissolution method employed throughout the examples and claims is in accordance with the method described in USP and Ph.Eur. method 2 (paddle) employing 0.1 N hydrochloric acid as dissolution medium, 500 ml of dissolution medium, 100 rpm, 37°C and the amount of midodrine (and/or desglylmidodrine) released was measured by UV at wavelength of 213.4.

time (hours)	core	core + 1 layer	core + 2 layers	core + 2 layers and coated
-----------------	------	-------------------	--------------------	-------------------------------

0,5	14,86	4.02		13.30
35 1		5.90	5.89	15.89

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2	26.26	9.38	9.06	20.15
3	32.10	14.94	11.68	23.75
4	36.24	25.59	13.83	27.12
6	42.48	44.47	17.91	36.23
5 8	45.02	56.66	21.93	52.70
10		63.07	33.67	70.52
12			40.17	85.40
15			56.02	95.67
18			76.08	96.81
10 20			82.46	

The dissolution profiles of the compositions tested are illustrated in Figs. 6-9 together with the release rate (% w/w dissolved/hour).

15 Example 2

Composition made by employment of triple compression

A tablet was prepared from the following ingredients:

20

Core:	Midodrine hydrochloride	1.66 mg
	Hydroxypropylmethyl cellulose E 50	48.34 mg
	Croscarmellose sodium	10.00 mg
		60.00 mg
1 st compression layer	Midodrine hydrochloride	0.62 mg
	Hydroxypropylmethyl cellulose E 15	126.38
	Hydroxypropylmethyl cellulose K 100	8
	LV	
		135.00 mg
2 nd compression layer	Midodrine hydrochloride	1.99 mg
	Hydroxypropylmethyl cellulose E 50	143.01 mg
		145.00 mg

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Using the core composition a core weighing 60 mg was compressed using a punch 6 mm in diameter. The core was compression coated using 135 mg of the 1st compression layer composition and a punch of 9 mm in diameter. The thus compression coated core was compression coated again using 145 mg of the 2nd compression layer composition and a punch of 11 mm in diameter.

A composition comprising midodrine hydrochloride 0.73 mg, hydroxypropylmethyl cellulose E 5 3.58 mg, Talc 2.51 mg and propylene glycol 0.71 mg was applied to the tablet by spray coating.

Finally a top coat comprising hydroxypropylmethyl cellulose E 5 1.79 mg, Talc 1.25 mg and propylene glycol 0.36 mg was applied to the tablet by spray coating.

15

The following results were obtained with respect to dissolution and release rate employing Dissolution Method I. The results are also shown in Figs. 17 and 18.

% w/w dissolved based on the total weight of the composition tested

20

Time [hours]	Core + 1 st + 2 nd compression layer (n = 2)		Core + 1 st + 2 nd compression layer + coating (n = 6) *	
	% dissolved	Release rate [%/h]	% dissolved	Release rate [%/h]
0.0	0.0	0.0	0.0	0.0
0.5	17.7	25.44	25.5	33.80
1.0	25.4	13.83	33.8	14.25
2.0	37.6	9.40	45.7	9.10
3.0	44.2	7.74	-	-
4.0	53.1	7.19	58.3	5.53
6.0	64.2	6.64	67.8	5.95
7.0	71.9	6.64	-	-
8.0	77.4	5.53	82.1	7.20
10.0	88.5	7.19	96.8	5.53
12.0	106.2	8.85	104.2	3.80

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* Data from the release of the product is shown

Example 3

5

Composition made as a coated matrix

The following compositions were prepared:

10	Composition 1:	<u>Core:</u>	
		Midodrine hydrochloride	10.0 mg
		Klucel LF	340.0 mg
		<u>Insoluble inner coat</u>	
15		Methocel E 5	0.2 mg
		Magnesium stearate	0.1 mg
		Talc Ponderax	0.4 mg
		Anti foam	4.8 µg
		Eudragit NE 30 D	4.5 mg
20		<u>Soluble outer coat</u>	
		Methocel E 5	1.8 mg
		Talc Ponderax	1.8 mg
25	Composition 2:	<u>Core:</u>	
		Midodrine hydrochloride	10.0 mg
		Klucel MF	340.0 mg
		<u>Insoluble inner coat</u>	
30		Methocel E 5	0.2 mg
		Magnesium stearate	0.1 mg
		Talc Ponderax	0.4 mg
		Anti foam	4.8 µg
		Eudragit NE 30 D	4.5 mg
35			

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Soluble outer coat

Methocel E 5

1.8 mg

Talc ponderax

1.8 mg

- 5 Cores of both composition 1 and composition 2 were compressed using a punch 10 mm in diameter. Core weighing 350 mg.

Both types of cores were coated with an insoluble inner coat and a soluble outercut. The release profile can be shifted up or down by changing the amount of weight increase of
10 cores when applying the inner coat.

If suitable, the release profile can be changed by coating with other acrylic resins such as Eudragit RL 30 D, Eudragit RS 30 D or combinations thereof, or using other types of film forming agents such as ethylcellulose or silicone polymers. Furthermore, the release
15 profile can be changed by using other types of matrix former such as acrylic resins, other types of cellulose ethers such as L-HPC (low-substituted hydroxypropylcellulose), HPC (hydroxypropylcellulose), HPMC (hydroxypropylmethylcellulose), HEC (hydroxyethylcellulose), MC (methylcellulose), HEMC (hydroxyethylmethylcellulose), EC (ethylcellulose) or other viscosity grades of HPC (hydroxypropylcellulose).

20 The following results were obtained with respect to dissolution and release rate (performed in accordance with the general method described herein):

25		% w/w dissolved based on the total weight of the composition tested			
time		comp. 1	comp. 1	comp. 2	comp. 2
(hours)			coated		coated
1		16.72	7.67	15.77	6.41
30 2		27.25	14.60	22.36	10.85
3		36.86	21.24		
4		45.66	27.59	32.14	19.62
6		60.37	38.18	36.26*	24.03*
8			49.10	49.13*	38.74*
35 10		80.74	59.82		

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12	87.09	69.74	54.44*	44.83*
15	91.37	81.48	63.06	54.89
18			66.70*	59.27*

5 * Time is 5, 9, 11 and 17 hours

The results are also shown in Figs. 10-13.

Example 4

10

Multilayer coating compositions

The following compositions were prepared:

15	Composition 1:	Core (Non pareil)	200 mg
		<u>1. coat</u>	
		Midodrine	4.0 mg
20		Methocel E 5 M	0.3 mg
		Magnesium Stearate	60.0 µg
		Talc ponderax	0.5 mg
		Anti foam	4.0 µg
		Eudragit NE 30 D	5.2 mg
25		<u>2. coat</u>	
		Midodrine	3.0 mg
		Methocel E 5 M	0.3 mg
30		Magnesium Stearate	60.0 µg
		Talc ponderax	0.5 mg
		Anti foam	4.0 µg
		Eudragit NE 30 D	6.1 mg
35		<u>3. coat</u>	

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5	Midodrine	2.0 mg
	Methocel E 5 M	0.3 mg
	Magnesium Stearate	80.0 µg
	Talc ponderax	0.6 mg
	Anti foam	6.0 µg
	Eudragit NE 30 D	7.1 mg
<u>4. coat</u>		
10	Midodrine	1.0 mg
	Methocel E 5 M	0.4 mg
	Magnesium Stearate	80.0 µg
	Talc ponderax	0.7 mg
	Anti foam	6.0 µg
	Eudragit NE 30 D	7.8 mg
<u>Outer coat</u>		
20	Methocel E 5	1.0 mg
	Talc ponderax	1.0 mg

Non-pareil beads were coated in four steps with four different films in a fluid bed coater.

- 25
1. film comprising 1. coat
 2. film comprising 2. coat
 3. film comprising 3. coat
 4. film comprising 4. coat.

- 30 A final layer of coating comprising the outer coat was applied and the films were cured at 70°C

Composition 2: Core (Non pareil) 200 mg

- 35 Non-pareil beads were coated in seven steps with four different films alternating with a

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blank film in a fluid bed coater.

The four different film formulations are similar to the four different film formulations in composition 1, the alternating coats are as follows:

5

Alternating coat

	Methocel E 5 M	0.2 mg
	Magnesium stearate	40.0 µg
10	Talc ponderax	0.3 mg
	Anti foam	2.0 µg
	Eudragit NE 30 D	3.5 mg

1. film comprising 1. coat
- 15 2. film comprising Alternating coat
3. film comprising 2. coat
4. film comprising Alternating coat
5. film comprising 3. coat
6. film comprising Alternating coat
- 20 7. film comprising 4. coat

A final layer of coating comprising outer coat in composition 1 was applied and the films were cured at 70°C.

Composition 3: Core (Non pareil) 200 mg

25

1. coat

	Midodrine	4.0 mg
	Paraffin, solid	0,3 mg
30	Acetyltributyl citrate	0.1 mg
	Ethylcellulose	1.9 mg
	Aerosil 200	28.0 µg

2. coat

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5	Midodrine	3.0 mg
	Paraffin, solid	0,3 mg
	Acetyltributyl citrate	0.1 mg
	Ethylcellulose	2.2 mg
	Aerosil 200	32.0 µg

3. coat

10	Midodrine	2.0 mg
	Paraffin, solid	0,4 mg
	Acetyltributyl citrate	0.1 mg
	Ethylcellulose	2.5 mg
	Aerosil 200	40.0 µg

15 4. coat

20	Midodrine	1.0 mg
	Paraffin, solid	0,4 mg
	Acetyltributyl citrate	0.2 mg
	Ethylcellulose	2.8 mg
	Aerosil 200	40.0 µg

Outer coats

25	Paraffin, solid	0,5 mg
	Acetyltributyl citrate	0.2 mg
	Ethylcellulose	3.3 mg
	Aerosil 200	50.0 µg

30

Non-pareil beads were coated in four steps with four different films in a fluid bed coater:

1. film comprising 1. coat
2. film comprising 2. coat
- 35 3. film comprising 3. coat

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4. film comprising 4. coat.

A final layer of coating comprising outer coats was applied.

- 5 The following results were obtained with respect to dissolution and release rate (performed in accordance with the general method described herein). The results are also shown in Figs. 14-16.

10 % w/w dissolved based on the total weight of the composition tested

	time (hours)	composition 1	composition 2	composition 3
15	0,5	26.02	19.84	5.41
	1	55.24	33.08	
	2	78.38	64.39	22.92
	3	85.01	77.64	35.52
	4	87.91	83.41	43.61
20	6	90.43	88.39	55.16
	8	91.61	90.63	61.75
	15			72.09

- If suitable, the release profile can be changed by coating with other acrylic resins such as Eudragit RL 30 D, Eudragit RS 30 D or combinations thereof, or using other types of film forming agents such as ethylcellulose or silicone polymers, or incorporating lipophilic compounds such as, e.g., stearic acid, capric acid or hydrogenated castor oil in the film.

Example 5

30

Preparation of a controlled release composition using commercially available filmforming agents

- The present example illustrates the preparation of a coated pellet composition. The aim was to prepare pellets having a release kinetic different from zero order release.

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Pellets were prepared from the following ingredients:

I	Midodrine hydrochloride	600.0 g
5 II	Microcrystalline cellulose (Type PH 101)	752.0 g
III	Lactose monohydrate	2608.0 g
IV	Sodium carboxymethylcellulose	40.0 g
V	Purified water	1120.0 g

- 10 I + II + III + IV are admixed in a Fielder intensive mixer at an appropriate time and mixing intensity.

V is applied to the mixture (I-IV) while mixing. When V is applied the mixing is continued at an appropriate time with an appropriate mixing intensity.

15

The wetted mass is extruded through a screen with apertures between 0.4 -1.0 mm.

The extrudate is spheronised until the surface of the resulting pellets is smooth.

- 20 An inner and an outer coating were applied:

Inner coat

The weight of the pellets is increased with 8.5% w/w.

25

I	Hydroxypropylmethylcellulose	13.5 g
II	Magnesium stearate	2.9 g
II	Talc	25.2 g
IV	Eudragit NE 30 D	895.1 g
30 V	Purified water	1135.4 g

The pellets are coated in a fluid bed with appropriate process parameters.

Immediately after the inner coat has been applied an outer coat is applied.

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Outer coat

The weight of the pellets is increased with 1% w/w.

5	I	Hydroxypropylmethylcellulose	20.0 g
	II	Talc	20.0 g
	III	Purified water	460.0 g

The pellets are coated in a fluid bed with appropriate process parameters.

10

The weight of 1 unit dose containing 30 mg midodrine hydrochloride is 219 mg.

15 The release profile can be shifted up or down by changing the amount of weight increase of pellets when applying the inner coat.

The release profile can be changed by mixing fractions of pellets with different amounts of inner coating applied or the release profile can be changed by coating with other acrylic resins such as Eudragit RL 30 D, Eudragit RS 30 D or combinations thereof, or using
20 other types of film forming agents such as ethylcellulose or silicone polymers.

Furthermore, the release profile can be changed by applying a fraction of non-coated pellets or by applying an enteric coating to a fraction of pellets.

25 Example 6

Preparation of a controlled release formulation using a film containing paraffin

The present example illustrates the preparation of a coated pellet composition. The aim
30 was to prepare pellets having a release kinetic different from zero order release.

Coated pellets were prepared from the following ingredients:

The composition and manufacturing process of pellets are similar to Example 5.

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A coating was applied. Paraffin-containing film; the weight of the pellets is increased with 8% w/w.

I	Paraffin, solid	29.89 g
5 II	Acetyltributyl citrate	10.53 g
III	Ethyl cellulose	196.61 g
IV	Silicium dioxide (Aerosil 200)	2.95 g
V	Isopropyl alcohol	3970.03 g

10 The pellets are coated in a fluid bed with appropriate process parameters.

The weight of 1 unit dose containing 30 mg midodrine hydrochloride is 212 mg.

15 Example 7

Preparation of a controlled release composition having a zero order release

The present example illustrates the preparation of a coated beads composition. The aim
20 was to prepare beads having a zero order release kinetic.

Coated beads were prepared from the following ingredients:

Non dissolvable non-pareil beads of equal size are coated with a suspension of midodrine
25 hydrochloride. A diffusion barrier is coated on top of the midodrine hydrochloride layer, and thereby controlling the release of midodrine hydrochloride.

4000 g non-pareil beads having a uniform particle size in a range between 0.4 mm and 1.0 mm are transferred to a fluid bed coater.

30

The beads are coated with coating suspension 1 (containing midodrine hydrochloride):

I	Hydroxypropylmethylcellulose	8.8 g
II	Magnesium stearate	1.9 g
35 III	Talc	16.5 g

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IV	Eudragit NE 30 D	585.1 g
V	Purified water	742.1 g
VI	Midodrine hydrochloride	200.0 g

5 The weight of the beads is increased with 10% w/w.

The beads are coated employing appropriate process parameters.

Immediately after coating suspension 1 has been applied a second coating suspension is
10 applied.

The beads are coated with coating suspension 2:

I	Hydroxypropylmethylcellulose	11.7 g
15 II	Magnesium stearate	2.5 g
III	Talc	21.7 g
IV	Eudragit NE 30 D	772.3 g
V	Purified water	979.6 g

20 The weight of the coated beads is increased with 6% w/w.

The pellets are coated employing appropriate process parameters.

Immediately after coating suspension 2 has been applied a third coating suspension is
25 applied.

The beads are coated with coating solution 3:

I	Hydroxypropylmethylcellulose	23.3 g
30 II	Talc	23.3 g
III	Purified water	536.8 g

The weight of the coated beads is increased with 1% w/w.

35 The beads are coated in a fluid bed employing appropriate process parameters.

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The weight of 1 unit dose containing 20 mg midodrine hydrochloride is 471 mg.

- 5 By changing the weight gain of the beads when applying the second coating suspension, the release profile can be shifted up or down.

- The release profile can be changed by mixing fractions of beads having different amounts of second coating suspension applied or the release profile can be changed by coating
10 with other acrylic resins such as Eudragit RL 30 D, Eudragit RS 30 D or combinations thereof, or using other types of film forming agents such as ethylcellulose or silicone polymers.

- The above-mentioned filmforming agents can also be combined with pore forming agents
15 such as cellulose ethers, polyols, PEG's.

Furthermore, the release profile can be changed by applying an enteric coating to a fraction of the coated beads.

20 Example 8

Preparation of a zero order controlled release composition

- The present example illustrates the preparation of a coated minitabiet composition. The
25 aim was to prepare coated minitabiet of equal size in order to obtain a zero order release kinetic.

Formulation of minitabiet:

30	I	Midodrine hydrochloride	800.0 g
	II	Dicalcium phosphate	2960.0 g
	III	Talc	100.0 g
	IV	Magnesium stearate	40.0 g
	V	Polyvinylpyrrolidone 90	100.0 g
35	VI	Purified water	800.0 g

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V is dissolved in VI.

I + II are transferred to a Fialder Intensive mixer and admixed at an appropriate time and 5 mixing intensity.

The mixture is wetted with the solution V + VI.

Granulation is performed at an appropriate time and mixing intensity.

10

The drying of the wet granulate is carried out in an Aeromatic fluid bed.

The dried granulate is passed through a suitable sieve. IV + V are sieved through a 0.3 mm sieve and admixed to the sieved particulate mixture in a cube mixer for 10 min.

15

The thus obtained particulate mixture is compressed into tablets weighing 15 mg.

A dose of 30 mg midodrine corresponds to 10 minitables.

20 Coating of the minitables:

The minitables are coated with inner and outer coatings corresponding to the description in Example 7.

25 By changing the weight gain of the minitables when applying the inner coat, the release profile can be shifted up or down

The release profile can be changed by mixing fractions of minitables having different amounts of inner coating applied or the release profile can be changed by coating with

30 other acrylic resin such as Eudragit RL 30 D, Eudragit RS 30 D or combinations thereof, or using other types of film forming agents such as ethylcellulose or silicone polymers.

The above mentioned filmforming agents can also be combined with pore forming agents such as, e.g., cellulose ethers, polyols, PEG's, etc.

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Further, re, the release profile can be changed by applying an enteric coating to a fraction of the coated minitabets.

Example 9

5

Preparation of a controlled release composition having a release kinetic different from that of zero order

Matrix minitablets:

10

I	Midodrine hydrochloride	800.0 g
II	Ethyl cellulose (10 μ m)	2960.0 g
III	Talc	200.0 g
IV	Magnesium stearate	40.0 g
15 V	Purified water	800.0 g

I + II are admixed in a Fielder intensive mixer at an appropriate time and mixing intensity.

The mixture is wetted with V while mixing at an appropriate mixing intensity.

20

The wetted mixture is granulated at an appropriate time and mixing intensity.

The drying of the wet granulate is carried out in an Aeromatic fluid bed.

25 The dried granulate is passed through a suitable sieve. III + IV are sieved through a 0.3 mm sieve and admixed to the sieved particulate mixture in a cube mixer for 10 min.

The thus obtained particulate mixture is compressed into tablets weighing 15 mg.

30 A dose of 30 mg of midodrine hydrochloride is contained in 10 minitablets.

If suitable, the release profile can be changed by using other cellulose ethers such as HPC, L-HPC, HPMC or combinations of thereof.

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The principle of a matrix composition may also be used for a single unit tablet containing the total amount of midodrine hydrochloride in one unit.

- In order to further increase the retardation of the dissolution of midodrine hydrochloride the minitabets may be coated according to Example 7. The amount of coating applied may be varied to shift the dissolution profile up or down.

Example 10

10 Preparation of a controlled release composition having release kinetic different from zero order

Matrix minitabets:

15	I	Midodrine hydrochloride	800.0 g
	II	Ethyl cellulose (10 µm)	2960.0 g
	III	Talc	200.0 g
	IV	Magnesium stearate	40.0 g
	V	Isopropyl alcohol	800.0 g

20

I + II are admixed in a Fielder intensive mixer at an appropriate time and mixing intensity.

The mixture is wetted with V while mixing at an appropriate mixing intensity.

- 25 The wetted mixture is granulated for an appropriate time and mixing intensity.

The drying of the wet granulate is carried out in an Aeromatic fluid bed.

- 30 The dried granulate is passed through a suitable sieve. III + IV are sieved through a 0.3 mm sieve and admixed to the sieved particulate mixture in a cube mixer for 10 min.

The thus obtained particulate mixture is compressed into tablets weighing 15 mg.

A dose of 30 mg of midodrine hydrochloride is contained in 10 minitabets.

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In order to further increase the retardation of the dissolution of meldonium hydrochloride the minitables may be coated according to Example 7. The amount of coating applied may be varied to shift the dissolution profile up or down.

5 Example 11

Composition made by employment of double compression

A tablet was prepared from the following ingredients:

10

1st compression layer	Midodrine hydrochloride	2.40 g
	Starch 1500	89.46 g
	Lactose monohydrate	180.00 g
	Eudragite RS 30 D	75.0 g
	Acetyl tributylcitrate	5.64 g
2nd compression layer	Midodrine hydrochloride	0.5 g
	Hydroxypropylmethyl-cellulose E 50	49.5 g

The granulate for 1st compression layer was prepared in the following way:

Midodrine hydrochloride and Starch 1500 was mixed by hand. This mixture and lactose
15 monohydrate was mixed in a Moulinex food processor for 30 sec.

The granulating fluid comprising Eudragit RS 30 D and acetyl tributylcitrate was mixed by stirring for 5 min.

20 The granulating fluid was applied to the powder mixture while mixing in the Moulinex food processor. The time for applying the granulating fluid was 45 sec.

Wet massing time for the moist powder mixture was 30 sec.

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The moist granulate was tray dried and the dried granulate was passed through a 1000 μ m screen.

The granulate for 2nd compression layer was prepared in the following way:

- 5 Midodrine hydrochloride and hydroxypropylmethyl cellulose E 50 was mixed by hand and finally passed through a 500 μ m screen.

A double compression tablet was prepared in the following way:

A shallow concave round punch 11 mm in diameter was used to compress the tablet.

- 10 250 mg of the granulate for 1st compression layer was weighed into the die and compressed gently to a loose compact. 200 mg of the granulate for 2nd compression layer was weighed on top the loose compact. The loose compact and the granulate for 2nd compression layer was compressed with a force of approx. 17 kN to form a coherent tablet.

15

After compression a release controlling film, a film containing midodrine hydrochloride and a blank film were applied to the tablets.

Example 12

20

Composition made in the form of capsules containing multiple units (MICAP) – EC pellets coated with 45% w/w dry matter

The midodrine controlled release product is prepared by manufacturing one type of pellet,

- 25 which afterwards is coated with different types of film coatings. The capsule ends up with 3 different types of pellets (one non-coated pellet, one CR-coated pellet and one EC-pellet).

Pellets preparation

30

The pellet is prepared by the use of an extrusion/spheronization technique. The ingredients are listed in Scheme 12-1.

Scheme 12-1:

Ingredients	Amount (g) pr. Batchsize
-------------	--------------------------

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Microcrystalline cellulose	2135.0
Lactose monohydrate	1207.5
Carmellose Sodium	70.0
Midodrine Hydrochloride	87.5
Purified water	2000.0

The ingredients are mixed and wetted in a Fielder high shear mixer in which the water is applied by a nozzle.

- 5 The wetted mass was extruded in a Nica E 140 extruder with a screen size of 600 μm (those pellets which is being used for non coated pellets and for CR-coating) or 800 μm (those pellets used for EC-coating). The extrudate was spheronized in a laboratory unit for 5 min. The pellets were dried in a laboratory scala fluid bed for approx. 75 min at 50°C.
- 10 The dried pellets used for non coated pellets and for CR-coating were screened through a screen of 700 μm and the dried pellets used for EC-coating were fractionated with a lower screen of 500 μm and a upper screen of 1000 μm .

Step 1 pellets (non coated pellets)

15

One batch of these pellets is not coated because it is used as an immediate release unit. The pellets are a part of the content in the capsule.

Step 2 pellets (CR-coated pellets)

20

One batch of these pellets is coated with an inner coat and an outer coat in a fluid bed (GPCG3) with a 0.8 mm spray nozzle and a spray pressure of 2.5 bar. The composition for the coating is shown in Scheme 12-2.

25 Scheme 12-2:

Ingredients	Amount (g) pr. batchsize
Inner coat (batchsize 2000g)	
Hypromellose (viscosity	13.1

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5cps)	
Purified water	1094.0
Magnesium stearate	2.7
Talc	26.2
Polyacrylate dispersion 30% (Eudragit NE30D)	864.0
Outer coat (batchsize 1000g)	
Hypromellose (viscosity 5cps)	40.0
Purified water	920.0
Talc	40.0

In the coating process the following amount of inner and outer coat were applied. The amount of dry matter applied calculated in percentage of the core weight also appears 5 from below.

Inner coat: 1788.1 g per 3000.0 g pellets (dry matter: 9% of the core weight)

Outer coat: 375.0 g per 3000.0 g pellets (dry matter: 1% of the core weight)

10 Throughout the coating process the bed temperature was maintained substantially in the interval from 20-25°C by adjustment of the liquid flow rate or the inlet temperature. The Inlet air temperature was kept at approximately 32°C. After the application of the coatings the coated pellets were cured at a bed temperature of approximately 70°C for 30 min. Then the pellets were screened through a screen 1.0 mm. Oversized material was
15 discarded.

Step 3 pellets (EC pellets)

One batch of these pellets is coated with an EC-coat in a fluid bed (Wurster technique) with a 0.8 mm spray nozzle and a spray pressure of 2.5 bar. The composition for the coating is shown in Scheme 12-3.

Scheme 12-3:

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Ingredients	Amount (g) pr. batchsize
Isopropyl alcohol	3852.0
Talc	100.0
Acetyltributyl citrate	99.2
Methacrylic acid – methyl methacrylate copolymer (1:2) (Eudragit S12.5)	3948.8

In the coating process the following amount of the coat were applied. The amount of dry matter applied calculated in percentage of the core weight also appears from below.

- 5 15,517.2 g per 3000.0 g pellets (dry matter: 45% of the core weight)

Throughout the coating process the bed temperature was maintained substantially in the interval from 30-38°C by adjustment of the liquid flow rate or the inlet temperature. The inlet air temperature was kept at approximately 49°C. After the application of the coating

- 10 the pellets were screened through a screen 1.3 mm. Oversized material was discarded.

Capsule filling

The 3 different pellets (steps 1, 2 and 3) were filled into capsules by hand. The amount of

- 15 pellets per capsule is shown in Scheme 12-4.

Scheme 12-4:

Unit	Amount (mg) per capsule
Capsule	approx. 76.3
Pellets step 1	approx. 50.4 corresp. to 1.25 mg midodrine hydrochloride
Pellets step 2	approx. 110.6 corresp. to 2.5 mg midodrine hydrochloride
Pellets step 3	approx. 72.7 corresp. to 1.25 mg midodrine hydrochloride
Total weight of capsule	approx. 310 corresp. to 5.0 mg midodrine hydrochloride

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Dissolution data

- 5 The following results were obtained with respect to dissolution and release rate employing Dissolution Method III

The mixture of the 3 types of pellets had the dissolution data shown in Scheme 12-5:

10

Scheme 12-5

Time (hours)	Capsule (n = 12)	
	% dissolved	Release rate (%/h)
0.0	0.0	0.00
0.5	29.9	33.26
1	33.3	6.63
2	39.8	7.00
3	47.3	7.84
4	55.5	8.31
6	72.3	7.02
7	77.9	10.00
8	92.3	7.92
10	95.2	1.30
12	97.5	1.15

The results are also shown in Fig. 19.

- In Fig. 20 is given the dissolution data for 4 different compositions having different content of midodrine hydrochloride. As is evident from the profiles, the dissolution is independent on the midodrine dose.

Example 13

- 20 Composition in the form of capsules containing multiple units (MICAP) – EC pellets coated with 35% w/w dry matter

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The following example illustrates that the amount of dry matter in the EC coating is very important in order to achieve a composition, which has the dissolution characteristics according to the requirements described herein. Thus, an EC coat containing 35% w/w dry matter is apparently not as suitable as an EC coat with 45% w/w dry matter (Example 12).

The midodrine controlled release product is prepared as in Example 12. The only difference is the amount of dry matter applied on the entero coated pellets.

10

Pellets preparation

As described in Example 12

Step 1 pellets (non coated pellets)

15 As described in Example 12

Step 2 pellets (CR-coated pellets)

As described in Example 12

20 **Step 3 pellets (EC pellets)**

The composition for the coating and the coating procedure are the same as those being used in Example 12 (except the amount of dry matter applied on the pellets).

In the coating process the following amount of the coat were applied. The amount of dry matter applied calculated in percentage of the core weight also appears from below.

12,069.0 g per 3000.0 g pellets (dry matter: 35% of the core weight)

Capsule filling

30 The amount of pellets per test is shown in Scheme 13-1

Scheme 13-1:

Unit	Amount (mg) per capsule
Pellets step 1	approx. 50.4 corresponding to 1.25 mg midodrine hydrochloride

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Pellets step 2	approx. 110.6 corresponding to 2.5 mg midodrine hydrochloride
Pellets step 3	approx. 67.6 corresponding to 1.25 mg midodrine hydrochloride

Dissolution data

- 5 The following results were obtained with respect to dissolution and release rate employing Dissolution Method III.

The mixture of the 3 types of pellets had the dissolution data shown in Scheme 13-2:

10

Scheme 13-2

Time (hours)	Capsule (n = 6)	
	% dissolved	Release rate (%/h)
0.0	0.0	0.00
0.5	28.9	32.00
1	32.0	6.09
2	37.9	8.98
3	50.0	16.06
4	70.0	14.94
6	89.7	5.30
7	90.4	2.14
8	94.0	2.56
10	97.2	1.50
12	100.0	1.40

The results are also shown in Fig. 21.

Example 14

15

Composition made by employment of mixing a matrix granulate and a slow release granulate.

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250 mg of the granulate called 1st compression layer (slow release granulate) was mixed with 200 mg of the granulate called 2nd compression layer (matrix granulate).

6

The granulate mixture was placed in the die and the granulate was compressed with a compression force of approx. 17 kN to form a coherent tablet.

The film compositions and the applied amounts are equal the compositions and amounts applied in Example 11.

15

% w/w dissolved based on the total weight of the composition tested

20

	Tablet 1 (n= 1)		Tablet 2 (n= 1)	
Time [hours]	% dissolved	Release rate [%]	% dissolved	Release rate [%]
0.0	0	0.0	0	0.0
0.5	18	18.0	18	18.0
1.0	18	0.5	18	1.0
2.0	19	2.0	20	2.0
3.0	22	3.5	22	2.5
4.0	26	5.5	25	6.5
6.0	48	27.0	42	17.0
7.0	87	23.5	69	19.0
8.0	95	4.0	80	8.0
10.0	96	0.5	89	2.5
12.0	96	0.0	93	2.0

Figure 1

Diagram illustrating the experimental setup for measuring the effect of temperature on the rate of reaction between hydrogen peroxide and potassium iodide.

The diagram shows a test tube containing a mixture of hydrogen peroxide (H_2O_2) and potassium iodide (KI). The test tube is placed in a water bath maintained at a constant temperature ($T^\circ C$). A gas syringe is connected to the test tube to measure the volume of oxygen gas (O_2) produced over time.

The reaction is represented by the equation:

$$H_2O_2 \rightarrow H_2O + O_2$$

The rate of reaction is determined by measuring the volume of oxygen gas evolved over a fixed period.

Example 15

Introduction

Midodrine is a prodrug labeled for treatment of orthostatic hypotension. After absorption it is readily metabolized to desglymidodrine that acts as an agonist at the peripheral α -1 receptors in the smooth muscles of arteries and veins, but has no direct central nervous or cardiac effects. Its main effect is to increase the vascular tone thus increasing the total peripheral resistance and rising blood pressure. The pressor effect of midodrine is manifest within 20 to 90 minutes after oral administration of a single dose. This pressor effect usually persists for 3 to 6 hours. Doses used in clinical practise (10 mg t.i.d.) significantly increase standing blood pressure, thus alleviating symptoms of orthostatic hypotension.

The rationale of the development of a controlled release formulation is to reduce the number of dosings during the day and to avoid major changes in plasma concentration of desglymidodrine. This will increase compliance and reduces changes in severity of symptoms of orthostatic hypotension and thus possibly increase quality of life.

Two prototypes have been developed according to the present invention. One prototype "Micap" is a multiple unit formulation (see Example 12), each unit releasing its amount of 35 midodrine dependent on the acidity of the environment. As the acidity is different in

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Objective

Trial design

Trial population

Assessments

Whenever, the concentration went under the detection limit, the values were set to $\frac{1}{2} \times$ detection limit, i.e. for midodrine $\frac{1}{2} \times 1$ ng/ml and for desglymidodrine $\frac{1}{2} \times 0.5$ ng/ml.

35 Because of such a contribution to the AUC, AUC_{24} was often larger than AUC_{infty} .

Midodrine tablets 5 mg, Gutron from Nycomed, Denmark, midodrine controlled release formulation (pH dependent release) prepared as described in Example 12, 5 mg, and
5 midodrine controlled release formulation (time dependent release) prepared as described in Example 2, 5 mg.

The subjects were fasting from 8 hours before dosing until 3 hours post dosing. Water
10 was allowed until 1 hour before dosing. No alcoholic beverages or beverages containing
caffeine (coffee, tea or cola) are allowed from 8 hours before dosing until last blood
sample has been drawn (24 hours).

Meals were standardized throughout all 3 study visits and served according to the following schedule:

- 4 hours after dosing: lunch
- 20 7 hours after dosing: snack
- 10 hours after dosing: dinner
- 14 hours after dosing: snack

25 Two tablets or capsules of study drug (midodrine tablets, Mitab or Micap) (total dose 10 mg) were administered between 7.30 and 8.30 am. Administration of study drug is followed by at least three days washout.

30 Seven ml of venous blood were withdrawn immediately before dosing, and at 15 and 30 minutes, 1, 1.5, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 20 and 24 hours after dosing. The blood samples were placed on ice immediately after drawing and centrifuged and frozen within 20 minutes. Analysis for midodrine and desglylmidodrine was performed by HPLC with fluorescence detection. The analyses were performed by Quintiles AB, Uppsala, Sweden.

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Results

The mean plasma concentration curves for midodrine and desglymidodrine, respectively, are shown in Figs. 24 and 25. The measured and calculated parameters for each composition (n= 7 for Micap and Mitab, n= 9 for standard tablets) are given in the following.

AUC and MRT have been calculated using the trapezoidal rule and the AUMC method (Yamaoka K., Nakagawa T., Uno T.: Statistical moments in pharmacokinetics, J.

10 Pharmacokin. Biopharm. 1978;6:547-58).

For extrapolation to infinity (the tail) the following formulas have been used:

C_p/k_e (for AUC) and $nC_p/(k_e^2)$ (for AUMC)

15

Where C_p = the last measured plasma concentration

k_e = the elimination rate constant

N = the time for last data point with measurable concentrations.

20 Midodrine ng/ml, mean values (standard deviation):

	Micap	Mitab	Standard tablets
AUC ₂₄	32.8 (6.7)	32.7 (12.1)	51.7 (13.5)
C _{max}	10.0 (2.6)	12.8 (6.5)	41.4 (12.6)
t _{max}	0.7 (0.4)	0.9 (0.5)	0.5 (0.2)
25 MRT	3.0 (0.4)	2.3 (0.3)	1.0 (0.2)
HVD	2.6 (1.1)	1.5 (0.8)	0.9 (0.3)
t _{75% Cmax}	1.0 (1.0)	0.8 (0.6)	0.5 (0.1)
AUC _{infinity}	24.1 (6.7)	21.8 (13.1)	41.3 (14.0)

30 Desglymidodrine ng/ml, mean values (standard deviation):

	Micap	Mitab	Standard tablets
AUC ₂₄	106.0 (29.1)	92.7 (36.4)	114.4 (31.9)
C _{max}	11.4 (3.2)	8.7 (5.0)	21.7 (5.1)
t _{max}	5.0 (0.0)	2.9 (1.1)	1.4 (0.4)
35 MRT	9.5 (1.0)	11.8 (4.1)	4.7 (0.5)

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HVD	7.7 (0.4)	9.9 (4.1)	4.1 (0.4)
$t_{75\% C_{max}}$	3.4 (0.3)	4.4 (0.5)	2.1 (0.4)
AUC_{∞}	111.5 (33.9)	104.1 (36.9)	112.9 (32.5)

5 Sum of midodrine and desglymidodrine nmol/l, mean values (standard deviation):

	Micap	Mitab	Standard tablets
AUC_{24}	566.1 (145.6)	509.1 (195.2)	667.3 (176.4)
C_{max}	60.5 (14.5)	66.0 (29.7)	195.1 (51.9)
10 t_{max}	3.0 (1.7)	1.3 (0.9)	0.6 (0.2)
MRT	9.7 (1.0)	12.4 (4.5)	4.6 (0.6)
HVD	7.7 (0.8)	5.0 (2.5)	1.9 (0.8)
$t_{75\% C_{max}}$	4.4 (1.2)	1.8 (1.3)	0.9 (0.4)
AUC_{∞}	608.7 (172.8)	588.2 (190.1)	661.1 (183.3)

15

Midodrine nmol/l, mean values (standard deviation)

	Micap	Mitab	Standard tablets
AUC_{24}	112.7 (23.2)	112.5 (41.8)	178.0 (46.4)
20 C_{max}	34.3 (9.1)	43.9 (22.4)	142.3 (43.5)
t_{max}	0.7 (0.4)	0.9 (0.5)	0.5 (0.2)
MRT	3.0 (0.4)	2.3 (0.3)	1.0 (0.2)
HVD	2.6 (1.1)	1.5 (0.8)	0.9 (0.3)
$t_{75\% C_{max}}$	1.0 (1.0)	0.8 (0.6)	0.5 (0.1)
25 AUC_{∞}	83.0 (23.1)	74.9 (45.0)	142.1 (48.2)

Desglymidodrine nmol/l, mean values (standard deviation):

	Micap	Mitab	Standard tablets
AUC_{24}	453.4 (124.7)	396.6 (156.0)	489.4 (136.5)
30 C_{max}	48.6 (13.5)	37.4 (21.5)	92.9 (22.0)
t_{max}	5.0 (0.0)	2.9 (1.1)	1.4 (0.4)
MRT	9.5 (1.0)	11.8 (4.1)	4.7 (0.5)
HVD	7.7 (0.4)	9.9 (4.1)	4.1 (0.4)
$t_{75\% C_{max}}$	3.4 (0.3)	4.4 (0.5)	2.1 (0.4)
35 AUC_{∞}	477.2 (144.9)	445.4 (157.7)	483.3 (138.9)

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Furthermore, the time interval in which the concentration of midodrine, desglymidodrine or the sum of midodrine and desglymidodrine is at a constant value $\pm 40\%$ has been determined. The time interval is found by looking at all possible time intervals (using the 5 time points from the blood sampling) of all possible lengths. For each time interval the mean is calculated and it is checked whether all plasma concentration points in that time interval is lying within $\pm 40\%$ of the mean value. The time interval in question is the longest time interval for which all concentration points in the interval lie within the mean of the time interval $\pm 40\%$. In order to get a relevant interval the constant value minus 40% 10 has to be higher than the detection limit. The interval is calculated for each patient and the mean value of the length of time interval is given.

For example, for patient 1 the MICAP capsules gave a mean plasma concentration of desglymidodrine at 8.5 ng/ml in the time interval from 2 hours to 9 hours (i.e. a 7 hours 15 interval). In this period the maximum plasma concentration of desglymidodrine was measured as 11.8 ng/ml and the minimum plasma concentration as 5.5 ng/ml. Since 8.5 ng/ml + 40% is 11.9 ng/ml and 8.5 ng/ml - 40% is 5.1 ng/ml all measured plasma concentration points in that particular interval lie within the mean value $\pm 40\%$. Since this 20 resulting time interval for the MICAP capsules for patient 1 was 7 hours.

The following results were obtained:

Time interval (hours) where the concentration of midodrine lies at a constant value $\pm 40\%$:

25

Micap (n=7)	1.7
Mitab (n=7)	1.4
Standard tablets (n=8)	0.63

30 Time interval (hours) where the concentration of desglymidodrine lies at a constant value $\pm 40\%$:

Micap (n=7)	6.3
Mitab (n=7)	11.5
35 Standard tablets (n=8)	3.7

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Time Interval (hours) where the sum of the concentration of midodrine and desglymidodrine lies at a constant value $\pm 40\%$:

5 Micap (n=7)	7.5
Mltab (n=7)	11.9
Standard tablets (n=8)	3.5

The aim of the pilot study was to test the bioavailability of the two novel compositions and a standard Gutron tablet and to estimate whether the compositions are bioequivalent. Furthermore, the controlled release properties of the novel compositions as compared to the standard composition (Gutron tablet) can be depicted from the data generated.

The values of C_{max} and $AUC_{0-24} / AUC_{\infty}$ of the standard tablet are greater than the same values of each of the two prototypes considering the plasma values of midodrine, desglymidodrine and the sum of the two. It is expected that C_{max} is lower in controlled release compositions than in plain release compositions as this reflects a lesser degree of fluctuation of plasma values. This is one of the purposes of a controlled release composition. It is further supported by the prolongation of the time interval in which the plasma values of midodrine, desglymidodrine and the sum of the concentrations of the two lie at a constant value.

The sum of the plasma concentrations of midodrine and the active metabolite desglymidodrine reflects the total amount of drug absorbed into the blood stream. The values of T_{max} , W_{50} and $T_{>75\% C_{max}}$ ($W_{75\%}$) and MRT for this sum concentration are more than 2 times greater of the novel controlled release compositions than the values of the standard tablet. The prolongation of the above mentioned values means that the active drug substance resides in the plasma for a longer time period reducing the numbers of daily dosing needed. Thus, another purpose of a controlled release composition is fulfilled.

Conclusion

Based on the AUC values, the bioavailabilities of the novel controlled release compositions are lesser than the bioavailability of the standard tablet indicating that the

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content of active drug substance in the controlled release compositions should be increased to establish bioequivalence.

The novel compositions possess controlled release properties as compared to the standard tablet for reasons discussed above.

Example 16**Powder preparation e.g for use in a needle-free device**

10

Composition

I	Midodrine HCl	1000.0 g
---	---------------	----------

15

The particle size distributions for the ingredients should be appropriate for deposition of the composition through the skin e.g. 0.5 μ m to 10 μ m.

The powder is filled into a drug cassette, each containing 5 mg Midodrine HCl.

20

Suspending agents such as glucose, lactose, celluloses, starches (maize-, rice-, potato-), calcium phosphate or mixtures of these may be used.

Example 17

25

Liquid composition for use in a needle-free device**Composition**

30	I	Midodrine HCl	50.0 g
	II	Sodium edetate	0.5 g
		Disodium hydrogen phosphate dihydrate	2.0 g
		Sodium dihydrogen phosphate dihydrate	2.0 g
	III	Water for injection	900.0 g
35	IV	Water for injection	ad 1000.0 g

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I is dissolved in III upon continuous stirring. The remaining solid ingredients (II) are added to the solution one by one during continuous stirring. Following complete dissolution of the solids, purified water is added to a total weight of 1000.0 g.

5

The formulation is filtrated (0,22 µm) and is filled into glass devices with a piston (e.g. teflon) and a stopper (e.g. rubber (natural or synthetic substances))

Tonicity agents may be dextrose, glycerol, sorbitol, mannitol, potassium nitrate and

10 sodium sulphate decahydrate or mixtures thereof.

pH may be adjusted to the appropriate value by use of additional buffer salts such as citric acid, sodium citrate, and potassium dihydrogen phosphate or mixtures of these.

15 Example 18

Liquid compositions for pulmonal delivery

A. Pressurised metered-dose preparation for inhalation

20

Composition

I	Midodrine HCl	50.0 g
II	Norflurane	ad 1000.0 ml

25

I is dissolved or suspended in liquid II at low temperature during continuous agitation.

For suspensions, the particle size distribution should be appropriate for deposition of the composition in the lung, e.g. 0.5 µm to 10 µm.

The product is filled into suitable pressurised multi-dose containers delivering 100 µl pr.

30 dose.

Other propellants such as dichlorodifluoromethane, dichlorotetrafluoroethane and trichlorofluoromethane or mixtures of these may be used.

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Glidants such as oleic acid and derivatives and isopropyl myristate or mixtures of these may be used to reduce friction during administration.

B. Liquid for nebulisation

5

Composition

I	Midodrine HCl	2.5 g
II	Sodium edetate	0.5 g
10	Disodium hydrogen phosphate dihydrate	2.0 g
	Sodium dihydrogen phosphate dihydrate	2.0 g
III	Purified water	900.0 g
IV	Purified water	ad 1000.0 g

- 15 I is dissolved in III upon continuous stirring. The remaining solid ingredients (II) are added to the solution one by one during continuous stirring. Following complete dissolution of the solids, purified water is added to a total weight of 1000.0 g. The composition is filled into 2 ml ampoules or other suitable unit-dose containers.

- 20 Excipients may be added to increase the solubility of midodrine, such as polyethylene glycol, alcohol, glycofurol, phospholipids, poloxamer, polyoxyethylene castor oil derivatives, polysorbates, propylene glycol and cyclodextrins or combinations of these. Tonicity agents may be e.g dextrose, glycerol, sorbitol, mannitol, sodium chloride, potassium nitrate and sodium sulphate decahydrate or mixtures thereof.

25

pH may be adjusted to the appropriate value by use of additional buffer salts such as citric acid, sodium citrate, and potassium dihydrogen phosphate or mixtures of these.

Sufficient microbiological preservation may be achieved by addition of benzalconium chloride or parabenes. Suitable flavors can be added to the composition and the taste can

- 30 be further adjusted by use of sweeteners such as saccharin, acesulfame, aspartame, cyclamate salts or mixtures of these.

Example 19

- 35 Powder composition for pulmonary delivery

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Composition

I	Midodrine HCl	500.0 g
5 II	Glucose	500.0 g

The particle size distributions for the ingredients should be appropriate for deposition of the composition in the lung, e.g. 0.5 μm to 10 μm . I and II are carefully mixed and sieved. The powder is filled into capsules or other suitable unit-dose containers, each containing 10 mg of the composition.

Other suspending agents such as lactose, celluloses, starches (maize-, rice-, potato-) calcium phosphate or mixtures of these may be used.

15 Example 20

Nasal compositions

General description of a nasal composition

20

A nasal composition of midodrine is buffered, and tonicity adjusted and it can be delivered from a device, which may or may not require the presence of antimicrobial agents in the composition. The amount of midodrine reaching the systemic circulation may be increased by addition of absorption enhancer(s) to the composition.

25

The variability of a nasal composition

The total amount of absorption enhancers included in the composition will, typically, vary between 0.01% and 10%. However, some absorption enhancers may also serve as vehicles and thereby totally replace the content of water in the composition. One can include one, two or several absorption enhancing agents in the composition. The final nasal composition may be a homogenous liquid, a suspension, an emulsion, a gel or a powder. The dose administered intranasally may be adjusted by choice of the volume of the formulation, ranging from 10 μl to 250 μl per nostril or of the mass of the composition, ranging from 5 mg to 50 mg.

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Specific examples of nasal compositions**Example 20.1**

5

Nasal composition without absorption enhancer

Composition			Function of Ingr.
I	Midodrine hydrochloride	50.0 g	Active ingr.
10 II	Sodium edetate	0.5 g	Stabiliser
	Disodium hydrogen phosphate dihydrate	2.0 g	Buffer component
	Sodium dihydrogen phosphate dihydrate	2.0 g	Buffer component
III	Purified water	900.0 g	Solvent
IV	Purified water	ad to 1000.0 g	Solvent

15

I is dissolved in III upon continuous stirring. The remaining solid ingredients (II) are added to the solution one by one during continuous stirring. Following complete dissolution of the solids, purified water is added to a total weight of 1000.0 g.

20 The composition is filled into appropriate nasal spray devices delivering 100 µl pr.dose.

pH may be adjusted to the appropriate value by use of additional buffer salts such as citric acid, sodium citrate and potassium dihydrogen phosphate or mixtures of these. Sufficient microbiological preservation may be achieved by addition of benzalconium chloride,

25 sorbic acid or parabenes such as methylparaben, ethylparaben, propylparaben and butylparaben or mixtures of these.

Example 20.2**30 Nasal composition with absorption enhancer**

Composition			Function of Ingr.
I	Midodrine hydrochloride	50.0 g	Active ingr.
II	Sodium glycocholate	5.0 g	Abs. enhancer
35 III	Sodium edetate	0.5 g	Stabiliser

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	Disodium hydrogen phosphate dihydrate	2.0 g	Buffer component
	Sodium dihydrogen phosphate dihydrate	2.0 g	Buffer component
IV	Purified water	900.0 g	Solvent
V	Purified water	to 1000.0 g	Solvent

5

It is dissolved in IV, and I is added upon continuous stirring. The remaining solid ingredients (III) are added to the solution one by one during continuous stirring. Following complete dissolution of the solids, purified water is added to a total weight of 1000.0 g.

10 The composition is filled into appropriate nasal spray devices delivering 100 µl pr.dose.

One, two or several of the absorption enhancers sodium cholate, sodium deoxycholate, sodium taurocholate, sodium taurodeoxycholate, sodium glycodeoxycholate, α -cyclodextrin, β -cyclodextrin, γ -cyclodextrin, methyl cyclodextrin, hydroxypropyl- β -

15 cyclodextrin, dimethyl- β -cyclodextrin, sodium taurodihydrofusidate, phosphatidylcholines, chitin, chitosan, hyaluronic acid, polyethylene glycols, starch microspheres and dextran. microspheres may be included in the composition.

pH may be adjusted to the appropriate value by use of additional buffer salts such as citric

20 acid, sodium citrate and potassium dihydrogen phosphate or mixtures of these. Sufficient microbiological preservation may be achieved by addition of benzalconium chloride, sorbic acid or parabenes such as methylparaben, ethylparaben, propylparaben and butylparaben or mixtures of these.

25 General description of a composition containing liposomes

Liposomes, or lipid vesicles, are spherical self-closed structures composed of concentric bilayers that entrap part of the solvent or active drug substance in the central core or in the bilayer depending on the hydrophilicity of the active drug substance. Liposomes are

30 predominantly made of natural amphiphilic lipids, e.g. phospholipids. Liposomes are likely to enhance the penetration of the active ingredient into the mucosa such as, e.g. the nasal, buccal, oral, rectal or vaginal mucosa.

Description of the variability of a liposomal composition

35

[illegible]

Example 20.3

Composition			Function of ingr.	
15	I	Mildodrine hydrochloride	50.0 g	Active ingr.
		Disodium hydrogen phosphate dihydrate	2.0 g	Buffer component
		Sodium dihydrogen phosphate dihydrate	2.0 g	Buffer component
	II	Purified water	900.0 g	Solvent
	III	Purified water	to 1000.0 g	Solvent
20	IV	DSPC	300.0 g	Liposome forming
		CH	84.0 g	Liposome stabiliser/destabiliser

25

30 pH may be adjusted to the appropriate value by use of additional buffer salts such as citric acid, sodium citrate and potassium dihydrogen phosphate or mixtures of these. Sodium edetate may be added to the composition as stabiliser. Sufficient microbiological preservation may be achieved by addition of sorbic acid or parabenes such as methylparaben, ethylparaben, propylparaben and butylparaben. Propylene glycol (10%)

5 The volume of the dose can be between 10-250 μ l, preferably 100 μ l. The dose can also be administered by application of two puffs, one in each nostril.

Other vesicle forming lipids can also be used instead of DSPC in the lipid bilayer. These amphiphilic lipids may be cationic, anionic or neutral, such as DPPC, DLPC, DOPC, DSEPC, dialkyl (C_8 - C_{20}) sulfosuccinate or fatty alcohol ethoxylate (with alkyl chain length of C_8 - C_{20} and 4 to 6 ethoxy groups). The molecular amount of lipids compared to active compound can be optimised with different liposome building lipids.

CH can be replaced by cholesterol derivatives or any other stabiliser/destabiliser such as
15 alkyl (C_8-C_{20}) phosphate, alkyl (C_8-C_{20}) sulfate, alkyl (C_8-C_{20}) ethersulfate, alkyl (C_8-C_{20})
ether carboxylate. Further stabilisers/destabilisers can be employed such as stearyl
lysophosphatidyl choline, lysophosphatidylcholine, palmitoyl lysophosphatidyl choline and
didecanoyl phosphatidyl choline.

20 Example 21

Buccal compositions

General description of a buccal composition

25

A buccal formulation of midodrine is buffered and tonicity adjusted and can be delivered from a device, which may or may not require the presence of antimicrobial agents in the formulation. The amount of midodrine reaching the systemic circulation may be increased by addition of absorption enhancer(s) to the composition.

30

The variability of the buccal composition

The total amount of absorption enhancers included in the formulation will, typically, vary between 0.01% and 10%. However, some absorption enhancers may also serve as
35 vehicles and thereby totally replace the content of water in the formulation. One can

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include one, two or several absorption enhancing agents in the formulation. The final buccal formulation may be a homogenous liquid, a suspension, an emulsion, a gel or a powder. The dose administered buccally may be adjusted by choice of the volume of the formulation, ranging from 10 μ l to 500 μ l or the mass of the formulation, ranging from 5mg to 100mg.

Example 21.1

Buccal formulation with liposomes

10

Composition			Function of Ingr.
I	Midodrine hydrochloride	50.0 g	Active Ingr.
	Disodium hydrogen phosphate dihydrate	2.0 g	Buffer component
	Sodium dihydrogen phosphate dihydrate	2.0 g	Buffer component
15 II	Purified water	900.0 g	Solvent
III	Purified water	to 1000.0 g	Solvent
IV	DSPC	300.0 g	Liposome forming
	CH	84.0 g	Liposome stabiliser/destabiliser
20			

I is dissolved in II upon continuous stirring. Following complete dissolution of the solids, purified water is added to a total weight of 1000.0 g.

- 25 The dry mix of DSPC:CH (7 mol DSPC:2 mol CH) (IV) is dispersed in water, and dehydrated. The liquid composition containing midodrine hydrochloride is poured into the dehydrated DSPC:CH during vigorous stirring to rehydrate the mixture of DSPC:CH.

- pH may be adjusted to the appropriate value by use of additional buffer salts such as citric acid, sodium citrate and potassium dihydrogen phosphate or mixtures of these. Sodium edetate may be added to the composition as stabiliser. Sufficient microbiological preservation may be achieved by addition of sorbic acid or parabenes such as methylparaben, ethylparaben, propylparaben and butylparaben. Propylene glycol (10%) can be added to potentiate the antimicrobial activity of the parabens in the presence of some amphiphilics.
- 35

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30 Composition			Function of ingr.
I	Midodrine hydrochloride	50.0 g	Active ingr.
II	Sodium edetate	0.5 g	Stabiliser
	Disodium hydrogen phosphate dihydrate	2.0 g	Buffer component
	Sodium dihydrogen phosphate dihydrate	2.0 g	Buffer component
35 III	Purified water	900.0 g	Solvent

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IV Purified water to 1000.0 g Solvent

I is dissolved in III upon continuous stirring. The remaining solid ingredients (II) are added to the solution one by one during continuous stirring. Following complete dissolution of the solids, purified water is added to a total weight of 1000.0 g.

The composition is filled into appropriate buccal spray devices delivering 100 µl pr.dose. pH may be adjusted to the appropriate value by use of additional buffer salts such as citric acid, sodium citrate and potassium dihydrogen phosphate or mixtures of these. Sufficient microbiological preservation may be achieved by addition of benzalconium chloride, sorbic acid or parabenes such as methylparaben, ethylparaben, propylparaben and butylparaben or mixtures of these.

Example 21.3

15

Buccal composition with absorption enhancer

Composition			Function of ingr.
I	Midodrine hydrochloride	50.0 g	Active ingr.
20 II	Sodium glycocholate	5.0 g	Abs. enhancer
III	Sodium edetate	0.5 g	Stabiliser
	Disodium hydrogen phosphate dihydrate	2.0 g	Buffer component
	Sodium dihydrogen phosphate dihydrate	2.0 g	Buffer component
IV	Purified water	900.0 g	Solvent
25 V	Purified water	to 1000.0 g	Solvent

II is dissolved in IV, and I is added upon continuous stirring. The remaining solid ingredients (III) are added to the solution one by one during continuous stirring. Following complete dissolution of the solids, purified water is added to a total weight of 1000.0 g.

30

The composition is filled into appropriate buccal spray devices delivering 100 µl pr.dose.

One, two or several of the absorption enhancers sodium cholate, sodium deoxycholate, sodium taurocholate, sodium taurodeoxycholate, sodium glycodeoxycholate, α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, methyl cyclodextrin, hydroxypropyl-β-

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5 pH may be adjusted to the appropriate value by use of additional buffer salts such as citric acid, sodium citrate and potassium dihydrogen phosphate or mixtures of these. Sufficient microbiological preservation may be achieved by addition of benzalconium chloride, sorbic acid or parabenes such as methylparaben, ethylparaben, propylparaben and butylparaben or mixtures of these.

10

Example 22

Midodrine sublingual tablets

15 General description

Sublingual tablets are designed to give a fast disintegration in the mouth by the amount of saliva normally available in that region. The disintegration time is therefore very short or short and there may be additives, which promote saliva secreting in the composition.

20

A fast disintegration together with a high solubility of the drug substance give the possibility of a fast absorption through the mucous membrane of the mouth, especially under the tongue where the blood vessels run close to the surface.

25 Sublingual absorbed drugs avoid more or less the first pass liver metabolism.

Description of variability in sublingual compositions

Sublingual tablets may be prepared by mould technique, by direct compression or by
30 conventional wet granulation or dry granulation (e.g. roller compaction) of the ingredients.
As mentioned, taste improving substances may be added to promote saliva secretion.
This may include artificial sweeteners (cyclamate, saccharinsodium, aspartame, etc.),
natural sweeteners (saccharose, sorbitol, xylitol, etc.), weak organic acids (citric-, acetic-,
ascorbic acid, ect.) natural or artificial flavours (strawberry, black currant, ananas, apple,
35 orange, lemon, etc.) in the below mentioned compositions.

35 orange, lemon, etc.) in the below mentioned compositions.

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Example 22.1

			Function
5	I Midodrine hydrochloride	2.5 g	5.0 g Active Ingr.
	II Purified water		Solvent
	Ethanol 96% equal parts	q.s.	q.s. Moist. agent
	III Lactose	52.5 g	50 g Filler
	Mannitol	45 g	45 g Filler

10

The amounts of lactose and mannitol may be varied from 25 to about 100 g. Dose 100 mg (50-200 mg) corresponds to 2.5 or 5.0 mg midodrine hydrochloride of the two compositions, respectively.

15 Disintegration time is extremely short (2-5 sec).

II is prepared, and I is dissolved in II. The solution is incorporated in III to a homogenous mixture is achieved. More II may be added.

20 The moistured mass is spread on a suitable plate equipped with wholes into which the mass is pressed and which have a depth that gives the wanted dose of drug substance. The wet mass is pressed out of the wholes and allowed to dry before further handling. (Sublingual tablet preparation by mould-technique).

25 II may be replaced by mixtures of different volatile organic solvents and may have a water content of 0 - 90%. III may be replaced by different mixtures of soluble pharmaceutically acceptable excipients as sorbitol, mannitol, xylitol, maltodextrin, lycasin, lactitol etc.

Example 22.2

			Function
30	I Midodrine hydrochloride	2.5 g	5.0 g active Ingr.
	II Tablettose	55.0 g	55.0 g filler
	III Cellulose, microcryst. Type 102	10.0 g	10.0 g filler/binder
	IV Agar sieve 180	5.0 g	5.0 g disintegrant
35	V Magnesium stearate	0.5 g	0.5 g glidant/lubricant

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Talc 4.5 g 4.5 g glidant/lubricant

I is mixed with II and further with III, IV and V and compressed into tablets.

- 5 The amount of the filler, tablettose, may vary from 25 to 75 g, the filler/binder (cellulose) may vary from 5 to 25 g, the disintegrant from 1 to 15 g, magnesium stearate from 0.1 to 2.5 g and talc from 1.0 to 10 g.

- Mass weight of 73 mg corresponds to a dose of 2.5 mg or mass weight of 75.5 mg
10 corresponds to a dose of 5.0 mg midodrine hydrochloride in the two compositions, respectively.

Disintegration time is short (30 sec – 4 min).

- 15 Tablettose may be replaced by other qualities of lactose with good flowability. Agar may be replaced by other disintegrants as croscarmellose sodium/calcium or the like, crosspovidone, starch glycolate, alginates or other disintegrants. Magnesium stearate may be replaced by other glidants as different types of silica colloidal hydrous or anhydrous, Ca-stearate, stearic acid, sodium stearyl fumarate, cotton-seed oil,
20 hydrogenated vegetable oils or other suitable lipid substances as e.g. Myvatex.

Example 22.3

			Function
	I Midodrine hydrochloride	2.5 g 5.0 g	active Ingr.
25	II Maize starch	9.5 g 7.0 g	filler
	Lactose	66 g 66 g	filler
	III Povidone 30	2.5 g 2.5 g	binder
	IV Purified water	q.s. q.s.	solvent
	V Mannitol	36 g 36 g	filler/taste
30	VI Magnesium stearate	1.5 g 1.5 g	lubricant

I is mixed with II and granulated with III dissolved in IV. More IV may be added. After drying, V and VI are added and tablets are compressed.

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The amount of maize starch may vary from 5 to 15 g, lactose from 30 to 100 g, mannitol from 10 to 80 g, and magnesium stearate from 0.5 to 5 g.

Disintegration time is about 5 min.

5

Maize starch may be replaced by other suitable starches as rice- or potato starch.

Lactose may be replaced by maltodextrine, dextrin etc.

Povidone 30 may be replaced by povidone VA 64 or 90 or gelatine or pregelatinized starch or different types of cellulose (methylcellulose, hydroxypropyl cellulose etc.).

10 Mannitol may be replaced by sorbitol, xylitol, maltitol, maltodextrin, lactitol, etc.

Magnesium stearate may be replaced by other glidants as different types of colloidal silica hydrous or anhydrous, Ca-stearate, stearic acid, sodium stearyl fumarate, cotton-seed oil, hydrogenated vegetable oils or other suitable lipid substances as e.g. Myvatex.

15 Example 23

Midodrine melt tablets

General description of melt tablets

20

Melt-tablets are also referred to as fast/rapidly- disintegrating tablets, dispersing tablets and dissolving tablets. In this example, the term "melt-tablet" is applied.

Melt-tablets are a tablet dosage form for oral administration, one that disintegrates

25 instantaneously and releasing the drug, which dissolves or disperses rapidly in saliva and afterwards swallowed without the need for water. The drug is absorbed in the normal way.

Less frequently melt-tablets are designed to be absorbed through the buccal mucosa. In that case the bioavailability of the drug from the melt-tablet may be even greater than

30 observed for standard dosage forms. Further more side-effects may be reduced if they are caused by first-pass metabolites.

A description of the variability of the melt-tablets

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5 To ensure melt-tablets fast- disintegrating and dissolving attribute water must quickly progress into the tablet matrix to cause rapid disintegration and instantaneous dissolution of the tablet. Maximising the porous structure of the tablet matrix and incorporating appropriate disintegrating agent and/or highly water-soluble excipients in the tablet formulation are the basic approaches applied in the current melt-tablet technologies.

In the formulation the total amount of disintegrating agents and/or highly water-soluble excipients can vary between 5-80% (w/v) and the total amount of binding agents can vary between 0.05-5% (w/v). Water is used to ensure the porous structure. Sufficient microbiological preservatives (benzoic acid, methylparaben etc.) may be added to prevent

Taste improving agents may be added to promote saliva secretion. This may include artificial sweeteners (aspartame, cyclamate, saccharin etc.), natural sweeteners (sucrose, sorbitol, xylitol etc.) weak organic acids (citric-, ascorbic acid etc.), natural or artificial flavours (strawberry, black currant, pineapple, apple, orange, lemon etc.). Colouring agents may also be added to give the melt-tablets elegance and identity.

Permeation enhancers (sodium lauryl sulphate etc.) may be added to optimise the transmemucosal absorption and pH-adjusting excipients (hydrochloride, sodium hydroxide etc.) may be used to optimise the chemical stability of the drug. Collapse protecting agents (glycine etc.) to prevent the shrinkage of the tablet during lyophilisation process or during long-term storage.

Composition			Function of Ingredient
I	Mildodrine hydrochloride	5.0 g	Active
II	Maltodextrin	200 g	Water-soluble

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III	Xanthan gum	20 g	Binding agent
IV	Purified water	775 g	Solvent

II and III are dissolved in IV upon continuous stirring and I is added to the solution during stirring. Purified water is added to a total weight of 1000.0 gram.

- 5 The solution is filled in PVC blister with a diameter of 15 mm and a depth of 6 mm, so the resulting dose of midodrine hydrochloride is 5 mg pr. tablet.

The blisters are placed on the shelves of the freeze-dryer. Samples are frozen to -45°C at a rate of $0.5^{\circ}\text{C}/\text{min}$ and kept at this temperature for 1.5 hour. Primarily, drying is

- 10 performed by keeping the blisters for 8 hour at a pressure of 1 mbar, a shelf temperature of -10°C , and a condensor temperature of -60°C .

Reducing the pressure to 0.1 mbar, carrying out secondary drying and increasing the shelf temperature to 25°C . Secondary drying time is 6 hour. Lyophilisation is terminated

- 15 by venting the drying chamber with air.

II may be replaced by lactose, mannitol, dextrose, xylitol, fructose, sucrose, maltose, sorbitol etc. or mixtures of these. As disintegrating agent croscarmellose, crospovidone etc. may be added. Other excipients may also be used instead of III. These excipients

- 20 may be gelatine, tragacanth gum, agar, acacia, alginate, dextran, povidone, hydroxyethylcellulose etc. or mixtures of these.

Example 24**25 Midodrine rectal compositions****General description**

Rectal solution is a way of drug administration free of the condition of the patient. Further

- 30 a quite quick onset of effect is seen for some compositions. A major part of the absorbed dose do not undergo first pass metabolism, which in some cases may be of some advantage.

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Description of variability in composition

The amount of rectal solution to give one dose is kept on the small amount of 1-4 ml such as, e.g., 2.0 ml. This is to avoid any emptying reflex from the rectum mucosa. The solution will be dispensed in a suitable container as a single-dose syringer or sealed plastic tube. Both equipped with a suitable tip.

A solution with high content of pharmaceutical acceptable organic solvent to promote absorption have been chosen as one example, a simple aqueous isotonic solution as one, a simple slightly viscous aqueous isotonic as one example and finally a aqueous pH-adjusted aqueous isotonic solution has been chosen as the last example.

Example 24.1

				Function
15	Midodrine hydrochloride	1.25 g	2.50 g	active ingr.
	Glycerol 85%	500 g	500 g	solvent/abs. enhancer
	Purified water up to	1000 ml	1000 ml	solvent

One dose of 2.0 ml = 2.5 mg midodrine hydrochloride or 2.0 ml = 5.0 mg midodrine hydrochloride. Glycerol may be exchanged with glycofurol, polyethylene glycols 200 to 600, propylene glycol or similar non-irritant suitable solvent. The amount of glycerol may vary from about 200 to 800 g.

Example 24.2

25				Function
	Midodrine hydrochloride	1.25 g	2.50 g	active ingr.
	Sodium chloride	9.0 g	9.0 g	isotonic agent
	Propylis paraoxibenzoas	0.2 g	0.2 g	preservative
	Methylis paraoxibenzoas	0.8 g	0.8 g	preservative
30	Purified water up to	1000 ml	1000 ml	solvent

The mixture of paraoxibenzoates may be exchanged with other suitable preservatives.

Dose 2.0 ml = 2.5 mg midodrine hydrochloride or 2.0 ml = 5.0 mg midodrine hydrochloride

35

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Example 24.3

			Function
	Midodrine hydrochloride	1.25 g 2.50 g	active ingr.
	Propylis paraoxibenzoas	0.2 g 0.2 g	preservative
5	Methylis paraoxibenzoas	0.8 g 0.8 g	preservative
	Sodium carboxymethylcellulose	6.0 g 6.0 g	viscosity incr. agent
	Purified water up to	1000 ml 1000 ml	solvent

Dose 2.0 ml = 2.0 mg midodrine hydrochloride or 2.0 ml = 5.0 mg midodrine

- 10 hydrochloride. The amount of viscosity increasing agent may vary from about 2 to about 8 g.

Example 24.4

			Function
15	Midodrine hydrochloride	1.25 g 2.50 g	active ingr.
	Sodium acetate	1.0 g 1.0 g	buffer agent
	Sodium chloride	8.5 g 8.5 g	isotonic agent
	Propylis paraoxibenzoate	0.2 g 0.2 g	preservative
	Methylis paraoxibenzoate	0.8 g 0.8 g	preservative
20	Purified water up to	1000 ml 1000 ml	solvent

The mixture of parabenzoates may be exchanged by other suitable preservative.

Sodium acetate may be exchanged by other suitable pH regulating substance or a buffer mixture with pH in the interval of 7.0 – 8.0. The amount of buffer agent may vary from

- 25 about 0.5 to about 3.0 g.

Dose 2.0 ml = 2.5 mg midodrine hydrochloride or 2.0 ml = 5.0 mg

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CLAIMS

1. A pharmaceutical kit comprising

- 5 i) a controlled release pharmaceutical composition for oral use comprising midodrine (ST 1085) or a pharmaceutically acceptable salt thereof and/or its active metabolite desglymidodrine (ST 1059) or a pharmaceutically acceptable salt thereof, the composition being adapted to release midodrine and/or desglymidodrine in such a manner that a relatively fast peak or shoulder plasma concentration of desglymidodrine is obtained and
- 10 that a therapeutically effective plasma concentration of desglymidodrine is maintained for at least about 9 hours such as, e.g. at least about 10 hours, at least about 11 hours, at least about 12 hours, at least about 13 hours, or at least about 14 hours, and
- ii) a relatively fast onset pharmaceutical composition comprising midodrine (ST 1085) or a
- 15 pharmaceutically acceptable salt thereof and/or its active metabolite desglymidodrine (ST 1059) or a pharmaceutically acceptable salt thereof, the composition being adapted to provide midodrine and/or desglymidodrine in such a manner that a relatively fast therapeutically effective concentration of desglymidodrine is obtained after administration of the composition.
- 20
2. A kit according to claim 1, wherein the relatively fast peak plasma concentration of desglymidodrine from the controlled release pharmaceutical composition is obtained about 15 min - 6 hours such as, e.g. about 0.5-6 hours, about 1-6 hours, about 2-5.5 hours, or about 2.5-5.2 hours after oral administration.
- 25
3. A kit according to claim 1, wherein the plasma concentration of desglymidodrine from the controlled release composition is maintained at a therapeutically active level for about 4.5-14 hours such as, e.g. about 6-14 hours, about 7-14 hours, about 8-13 hours, about 9-13 hours, about 10-14 hours, about 10-13 hours, or for at least about 4.5 hours, at least
- 30 about 5 hours, at least about 6 hours, at least about 7 hours, at least about 8 hours, at least about 9 hours, at least about 10 hours, at least about 11 hours, at least about 12 hours, at least about 13 hours or at least about 14 hours.
4. A kit according to claim 1, wherein the plasma concentration of desglymidodrine from
- 35 the controlled release composition is maintained at a relatively constant level for about

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35 20-55% (47%) w/w is released about 3 hours after start of the test.

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25-75% such as, e.g., 25-65% (53%) w/w is released about 4 hours after start of the test,
 30-74% (66%) w/w is released about 6 hours after start of the test,
 40-85% (80%) w/w is released about 8 hours after start of the test,
 65-100% (93%) w/w is released about 10 hours after start of the test,
 5 90-110% (100%) w/w is released about 12 hours after start of the test.

11. A kit according to claim 6, wherein the release pattern of midodrine from the controlled release composition - when tested *in vitro* using Dissolution Method III or IV described herein and employing a basket according to USP and Ph. Eur, 100 rpm, a first dissolution medium with a pH of about 1.0 for the first 2 hours of the testing followed by a second dissolution medium with a pH of about 6.0 for the next 5.5 hours and finally a third dissolution medium with a pH of about 7.5 until the end of the testing, and a temperature of 37 °C - is:

15 1-15% w/w is released from the composition within the first 30 min after start of the test,
 10-35% (26%) w/w is released about 30 min after start of the test,
 15-40% (35%) w/w is released about 1 hour after start of the test
 20-50% (39%) w/w is released about 2 hours after start of the test,
 20-55% (47%) w/w is released about 3 hours after start of the test,
 20 25-75% such as, e.g., 25-65% (53%) w/w is released about 4 hours after start of the test,
 30-74% (66%) w/w is released about 6 hours after start of the test,
 40-95% such as, e.g., 45-85% (80%) w/w is released about 8 hours after start of the test,
 65-100% (93%) w/w is released about 10 hours after start of the test,
 75-110% (100%) w/w is released about 12 hours after start of the test.

25

12. A kit according to claim 6, wherein the release pattern of midodrine from the controlled release composition - when tested *in vitro* employing any of Dissolution Method I, II, III or IV as described herein, - is as follows ($\pm 30\%$ w/w such as, e.g., $\pm 25\%$, $\pm 20\%$, $\pm 15\%$ or $\pm 10\%$ of the values stated below):

30

about 25% w/w is released about 30 min after start of the test,
 about 35% w/w is released about 1 hour after start of the test,
 about 39% w/w is released about 2 hours after start of the test,
 about 47% w/w is released about 3 hours after start of the test,

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35 50-74% (66%) w/w is released about 6 hours after start of the test.

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60-85% (75%) w/w is released about 7 hours after start of the test,
70-95% (90%) w/w is released about 8 hours after start of the test,
80-100% (97%) w/w is released about 10 hours after start of the test,
90-110% (100%) w/w is released about 12 hours after start of the test.

5

15. A kit according to claim 6, wherein the release pattern of midodrine from the controlled release composition - when tested *in vitro* employing any of Dissolution Method I, II, III or IV as described herein - is as follows ($\pm 30\%$ w/w, $\pm 20\%$ w/w, $\pm 10\%$ w/w, $\pm 7.5\%$ w/w or $\pm 5\%$ w/w of the values stated below):

10

about 25% w/w is released about 30 min after start of the test,
about 35% w/w is released about 1 hour after start of the test,
about 39% w/w is released about 2 hours after start of the test,
about 47% w/w is released about 3 hours after start of the test,
about 53% w/w is released about 4 hours after start of the test,
about 66 w/w is released about 6 hours after start of the test,
about 75% w/w is released about 7 hours after start of the test,
about 80% w/w is released about 8 hours after start of the test,
about 90% w/w is released about 10 hours after start of the test,
about 100% w/w is released about 12 hours after start of the test.

16. A kit according to claim 6, wherein the release pattern of mldodrln from the controlled release composition - when tested *in vitro* employing any of Dissolution Method I, II, III or IV as described herein - is as follows ($\pm 30\%$ w/w, $\pm 20\%$ w/w, $\pm 10\%$ w/w, $\pm 7.5\%$ w/w or $\pm 5\%$ w/w of the values stated below):

about 28% w/w is released about 30 min after start of the test,
about 35% w/w is released about 1 hour after start of the test,
about 41% w/w is released about 2 hours after start of the test,
about 45% w/w is released about 3 hours after start of the test,
about 55% w/w is released about 4 hours after start of the test,
about 70 w/w is released about 6 hours after start of the test,
about 78% w/w is released about 7 hours after start of the test,
about 90% w/w is released about 8 hours after start of the test,
about 95% w/w is released about 10 hours after start of the test.

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17. A kit according to claim 6, wherein the release pattern of midodrine from the controlled release composition - when tested *in vitro* employing any of Dissolution Method I, II, III or IV as described herein - is as follows ($\pm 30\%$ w/w, $\pm 20\%$ w/w, $\pm 10\%$ w/w, $\pm 7.5\%$ w/w or $\pm 5\%$ w/w of the values stated below):

about 20% w/w is released about 30 min after start of the test,
about 20% w/w is released about 1 hour after start of the test,
about 20% w/w is released about 2 hours after start of the test,
about 20% w/w is released about 3 hours after start of the test,
about 25% w/w is released about 4 hours after start of the test,
about 45 w/w is released about 6 hours after start of the test,
about 75% w/w is released about 7 hours after start of the test,
about 90% w/w is released about 8 hours after start of the test,
about 95% w/w is released about 10 hours after start of the test,
about 100% w/w is released about 12 hours after start of the test.

18. A kit according to claim 1 containing desglymidodrine or a pharmaceutically acceptable salt thereof and wherein the release pattern of desglymidodrine from a controlled release composition follows the patterns claimed for midodrine in any of claims 10-17.

19. A kit according to claim 1 containing midodrine or a pharmaceutically acceptable salt thereof and desglymidodrine or a pharmaceutically acceptable salt thereof and wherein the release pattern of the sum of midodrine and desglymidodrine calculated on a molar basis from a controlled release composition follows the patterns claimed for midodrine in any of claims 10-17.

20. A kit according to claim 6, wherein the release rate of midodrine - when tested *in vitro* employing any of Dissolution Method I, II, III or IV - follows a curve which has a shape corresponding to

i) a relatively fast first initial release followed by
ii) a steady release or a slower release than in step i) above, which is followed by
iii) a second rise in release rate and, finally,

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21. A kit according to claim 20, wherein the second rise in release rate from the controlled release composition takes place 5-10 hours such as, e.g., about 5-9 hours, about 6-8 hours after start of the dissolution test.

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24. A kit according to claim 20, wherein the steady release from the controlled release
15 composition is maintained for at least 2 hours such as, e.g. at least 3 hours, at least 4
hours, at least 5 hours, at least 6 hours, at least 7 hours, at least 8 hours such as about 6-
8 hours.

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about 35 %/hour about 30 min after start of the test (range e.g. 15-40 %/hour),
about 12 %/hour about 1 hour after start of the test (range e.g. 4-15 %/hour),
about 6 %/hour about 2 hours after start of the test (range e.g. 2-10 %/hour),
about 7 %/hour about 3 hours after start of the test (range e.g. 2-10 %/hour),
30 about 6.5 %/hour about 4 hours after start of the test (range e.g. 2-15 %/hour),
about 7.5 %/hour about 6 hours after start of the test (range e.g. 2-30% such as, e.g., 2-10 %/hour),
about 10 %/hour about 8 hours after start of the test (range e.g. 2-15 %/hour),
about 2 %/hour about 10 hours after start of the test (range e.g. 0-10 %/hour),
35 about 1 %/hour about 12 hours after start of the test (range e.g. 0-10 %/hour).

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26. A kit according to claim 1 containing desglymidodrine or a pharmaceutically acceptable salt thereof and wherein the release rate of desglymidodrine from the controlled release composition follows the patterns claimed for midodrine in any of claims 5 20-25.

27. A kit according to claim 1 containing midodrine or a pharmaceutically acceptable salt thereof and desglymidodrine or a pharmaceutically acceptable salt thereof and wherein the release rate from the controlled release composition of the sum of midodrine and 10 desglymidodrine calculated on a molar basis follows the patterns claimed for midodrine in any of claims 20-25.

28. A kit according to any of the preceding claims for administration once or twice daily.

15 29. A kit according to claim 6, wherein the W_{50} of midodrine (defined as corresponding to the time the plasma concentration curve is or is above 50% of the C_{max} value) from the controlled release composition is from about 1 to about 9 hours such as, e.g. from about 1.3 to about 8 hours such as, e.g. at least about 1.4 hours, at least about 1.5 hours, or at least about 1.7 hours.

20

30. A kit according to any of the preceding claims, wherein the W_{50} of desglymidodrine (defined as corresponding to the time the plasma concentration curve is or is above 50% of the C_{max} value) from the controlled release composition is from about 5 to about 12 hours such as, e.g. from about 6 to about 11 hours such as, e.g. at least about 7 hours.

25

31. A kit according to any of the preceding claims, wherein T_{max} for the controlled release composition is increased with a factor of at least 2 when compared with a plain Gutron® tablet administered in the same dose and where T_{max} is determined from a plasma concentration versus time curve and the plasma concentration reflects the sum 30 concentration in nmol/l of midodrine and desglymidodrine.

32. A kit according to any of the preceding claims, wherein MRT (mean residence time) for the controlled release composition is increased with a factor of at least 1.5 such as, e.g., at least 2 when compared with a plain Gutron® tablet administered in the same dose 35 and where MRT is determined from a plasma concentration versus time curve and the

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plasma concentration reflects the sum concentration in nmol/l of midodrine and d sglymidodrine.

33. A kit according to any of the preceding claims, wherein W_{50} is increased with a factor of at least 2 such as, e.g., at least 2.5 when compared with a plain Gutron® tablet administered in the same dose and where W_{50} is determined from a plasma concentration versus time curve and the plasma concentration reflects the sum concentration in nmol/l of midodrine and desglylmidodrine after administration of the controlled release composition.

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34. A kit according to any of the preceding claims, wherein W_{75} ($T > 75\% T_{max}$) is increased with a factor of at least 1.5 such as, e.g., at least 2 when compared with a plain Gutron® tablet administered in the same dose and where W_{75} ($T > 75\% T_{max}$) is determined from a plasma concentration versus time curve and the plasma concentration reflects the sum concentration in nmol/l of midodrine and desglymidodrine after administration of the controlled release composition.

35. A kit according to any of the preceding claims, wherein the MRT for midodrine from the controlled release composition is at least about 1.5 hours such as, e.g., at least about 2 hours, at least about 2.5 hours or at least about 3 hours.

36. A kit according to any of the preceding claims, wherein the MRT for desglymidodrine from the controlled release composition is at least about 6 hours such as, e.g., at least about 7 hours, at least about 7.5 hours, at least about 8 hours, at least about 8.5 hours or
25 at least about 9 hours.

37. A kit according to any of the preceding claims, wherein midodrine is present in the form of (\pm)-2-amino-N-(β -hydroxy-2,5-dimethoxyphenethyl)acetamide, (+)-2-amino-N-(β -hydroxy-2,5-dimethoxyphenethyl)acetamide, (-)-2-amino-N-(β -hydroxy-2,5-dimethoxyphenethyl)acetamide or mixtures thereof.

38. A kit according to any of the preceding claims, wherein midodrine is present in the racemic form (RS), in the enantiomeric form (R), in the enantiomeric form (S) or in mixtures thereof.

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39. A kit according to claim 37 or 38, wherein at least 90% w/w such as, e.g., at least 95% w/w, at least 97% w/w, at least 98% w/w, at least 99% w/w of midodrine is present in the therapeutically active enantiomeric form.

5 40. A kit according to claim 39, wherein the therapeutically active enantiomeric form of midodrine is (-)-2-amino-N-(β -hydroxy-2,5-dimethoxyphenethyl)acetamide or the (R) form of midodrine.

41. A kit according to claim 1 containing the active metabolite desglymidodrine (ST 1059),
10 wherein desglymidodrine is present in the form of (\pm)- α -(aminomethyl)-2,5-dimethoxy-
benzenemethanol (\pm ST 1059), (+)- α -(aminomethyl)-2,5-dimethoxy-benzenemethanol (+
ST 1059), (-)- α -(aminomethyl)-2,5-dimethoxy-benzenemethanol
(- ST 1059), or mixtures thereof.

15 42. A kit according to claim 41, wherein desglymidodrine is present in the racemic form (RS), in the enantiomeric form (R), in the enantiomeric form (S) or in mixtures thereof.

43. A kit according to claim 41 or 42, wherein at least 90% w/w such as, e.g., at least 95% w/w, at least 97% w/w, at least 98% w/w, at least 99% w/w of desglymidodrine is present in the therapeutically active enantiomeric form.

44. A kit according to claim 43, wherein the therapeutically active enantiomeric form of desglymidodrine is (-)- α -(aminomethyl)-2,5-dimethoxy-benzenemethanol (- ST 1059) or the (R) form of desglymidodrine ((R) ST 1059).

25

45. A kit according to any of the preceding claims, wherein midodrine and/or desglymidodrine are present in the form of a pharmaceutically acceptable salt such as a salt formed between midodrine and/or desglymidodrine and an inorganic acid such as e.g., a hydrochloride, a hydrobromide, a hydroiodide, a nitrate, a nitrite, a H_3PO_3 salt, a H_3PO_4 salt, a H_2SO_3 salt, a sulfate, a H_2SO_6 salt, or a salt formed between midodrine and/or desglymidodrine and an organic acid such as organic acids like e.g. H_2CO_3 , acetic acid, C_2H_5COOH , C_3H_7COOH , C_4H_9COOH , $(COOH)_2$, $CH_2(COOH)_2$, $C_2H_5(COOH)_2$, $C_3H_6(COOH)_2$, $C_4H_8(COOH)_2$, $C_5H_{10}(COOH)_2$, fumaric acid, maleic acid, lactic acid, citric acid, tartaric acid, ascorbic acid, benzoic acid, salicylic acid and phthalic acid.

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46. A kit according to any of the preceding claims, wherein at least one of the controlled release and the relatively fast release composition is in liquid form.

47. A kit according to any of claims 1-45, wherein at least one of the controlled release
5 and the relatively fast release composition is in the form of a solid dosage form.

48. A kit according to claim 47, wherein at least one of the controlled release and the relatively fast release composition is in the form of tablets, capsules, sachets, solid dispersion, crystals and the like.

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49. A kit according to claim 48, wherein the controlled release composition comprises at least two parts such as at least a first and a second part, each part contains midodrine and/or, if present, desglymidodrine and the first part being adapted to release midodrine and/or, if present, desglymidodrine, in a controlled manner during the first 0-14 such as,
15 e.g. 0-11 hours or 0-8 hours after oral intake and the second part being adapted to release midodrine and/or, if present, desglymidodrine, starting at least 6 hours after oral intake.

50. A kit according to claim 49, wherein at least one of the at least two parts is present in
20 the composition in the form of a multiplicity of individual units such as, e.g. pellets or minitabets.

51. A kit according to claim 49, wherein the two parts of the at least two parts are present in the composition in the form of a multiplicity of individual units such as, e.g. pellets or
25 minitabets, and the two parts are in admixture.

52. A kit according to claim 49 in multiple unit dosage form.

53. A kit according to claim 52 in the form of a multiple unit dosage form, wherein at least
30 one of the at least two parts comprising at least two different types of pellets, the first type of pellets corresponding to a first fraction and the second type of pellets corresponding to a second fraction.

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54. A kit according to claim 52, wherein the at least two parts of the composition comprise at least two different types of pellets, the first type of pellets corresponding to the first part and the second type of pellets corresponding to the second part.

55. A kit according to claim 52 in the form of a multiple unit dosage form comprising at least two different types of minitables, the first type of minitables corresponding to the first part and the second type of minitables corresponding to the second part.

56. A kit according to claim 52 in the form of a multiple unit dosage form, wherein the first or the second part is in the form of minitables.

57. A kit according to claim 52, wherein the first or the second part is in the form of pellets.

58. A kit according to claim 49, wherein the at least two fractions is present in a tablet.

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59. A kit according to claim 58, wherein the tablet is a multilayer tablet and the at least first and the second part are each comprised in a layer in the tablet.

60. A kit according to claim 49 further comprising a third part adapted to release midodrine and, if present, desglymidodrine relatively fast from the composition.

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61. A kit according to claim 49 further comprising a fourth part adapted to release midodrine and/or desglymidodrine from the composition 6-10 hours after oral intake.

62. A kit according to claim 49 further comprising a fourth part adapted to release midodrine and/or desglymidodrine from the composition in the colon after oral intake.

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63. A kit according to claim 61 or 62, wherein the third and/or, if present, the fourth part comprise pellets or minitables or are a layer in or on a tablet.

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64. A kit according to claim 49, wherein the first part has a release kinetic corresponding to a zero or a first order release, a mixture of zero and first order release, or any other order of release such as, e.g. 1st, second, third or fourth order release.

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65. A kit according to claim 49 wherein the second part has a release kinetic corresponding to a zero or a first order release, a mixture of zero and first order release, or any other order of release such as, .g. 1½, second, third or fourth order release.

10 substances.

67. A kit according to any of claims 1-66, wherein at least one of the controlled release and the relative fast release composition comprises one or more further active drug substances.

68. A kit according to any of the preceding claims, wherein the relatively fast onset composition or part of the kit results in a peak or shoulder plasma concentration within 90 minutes such as, e.g., within 60 minutes, within 45 minutes, within 30 minutes, or within 15 20 minutes upon administration of the relatively fast onset composition.

69. A kit according to any of the preceding claims, wherein the relatively fast onset composition is a nasal composition.

20 70. A kit according to claim 69, wherein the nasal composition comprises polyethyleneglycol and/or glycofurool as a nasal vehicle.

71. A kit according to claim 70, wherein the polyethyleneglycol is PEG 200 and/or PEG 300.

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72. A kit according to any claims 1-69, wherein the relatively fast onset composition is in the form of a liposomal composition.

73. A kit according to any of claims 1-69, wherein the relatively fast onset composition is
30 in the form of tablets such as, e.g., melt tablets or sublingual tablets.

74. A kit according to any of claims 1-69, wherein the relatively fast onset composition is a buccal, oral, or rectal composition.

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89. A method according to any of claims 82-85, wherein the administration of the relatively fast onset composition takes place 1- 6 times daily.

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Abstract

Novel pharmaceutical kit comprising a controlled release pharmaceutical compositions for oral use containing midodrine and/or its active metabolite desglymidodrine and a relatively fast onset composition. The controlled release compositions are designed to release midodrine and/or desglymidodrine after oral intake in a manner which enables absorption to take place in the gastrointestinal tract so that a relatively fast peak plasma concentration of the active metabolite desglymidodrine is obtained followed by a prolonged and relatively constant plasma concentration of desglymidodrine.

The controlled release compositions may be designed for administration once or twice daily, i.e. a therapeutically effective concentration of desglymidodrine is maintained for a period of at least 10-16 hours followed by a wash out period of about 8-12 hours in order to avoid the well-known midodrine related side effect with respect to supine hypertension. The therapeutically effective concentration of desglymidodrine is regarded as a plasma concentration of desglymidodrine of at least about 3 ng/ml. A composition is designed to release midodrine and/or desglymidodrine in at least the following consecutive steps: i) an initial relatively fast release of midodrine and/or desglymidodrine (in order to obtain a relatively fast onset of action), ii) a steady release or a slower release than in step 1 of midodrine and/or desglymidodrine (in order to maintain a plasma concentration of desglymidodrine which is prolonged and relatively constant), iii) a second rise in release of midodrine and/or desglymidodrine (in order to take advantage of absorption from the colon, i.e. such a second rise release is designed to take place when the composition (or the disintegrated parts of the composition) reaches the colon; normally this is regarded to take about 8 hours after oral intake, and iv) a decline in release rate corresponding to that essentially all midodrine and/or desglymidodrine have been released from the composition.

One of the advantages of the invention is that the controlled release composition provides a base line plasma concentration, which during most of the day is therapeutically effective. When a higher concentration is needed, only a minor supply of active drug substance is necessary to obtain a very fast relief from symptoms. If the constant base line plasma concentration was absent, it would be necessary to use a relative higher fast onset dose to reach the high therapeutically effective level. The kit

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Also disclosed is a method for treating orthostatic hypotension and/or urinary incontinence, the method comprising administration to a patient in need thereof of an effective amount of midodrine and/or desglymidodrine in a kit according to the invention.

SECRET

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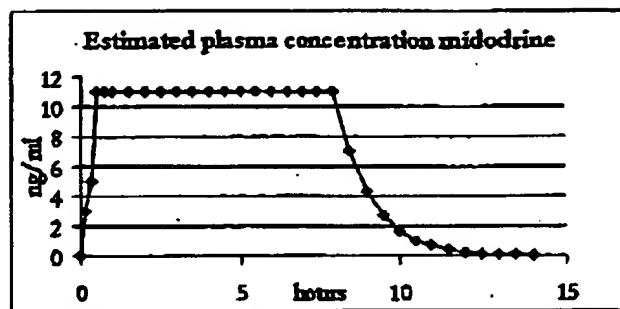


Fig. 1

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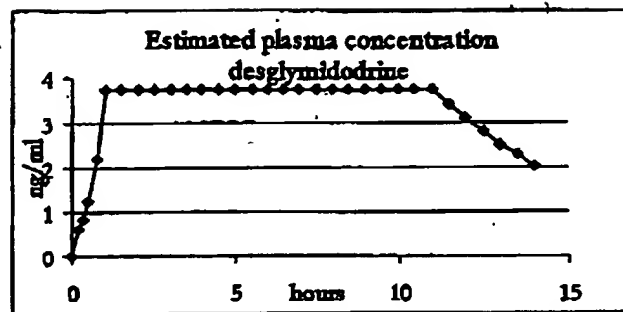


Fig. 2

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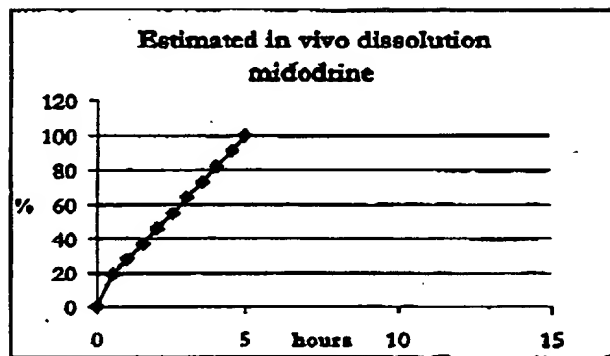


Fig. 3

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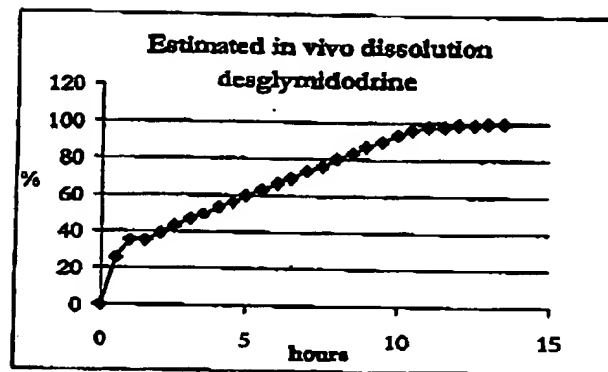


Fig. 4

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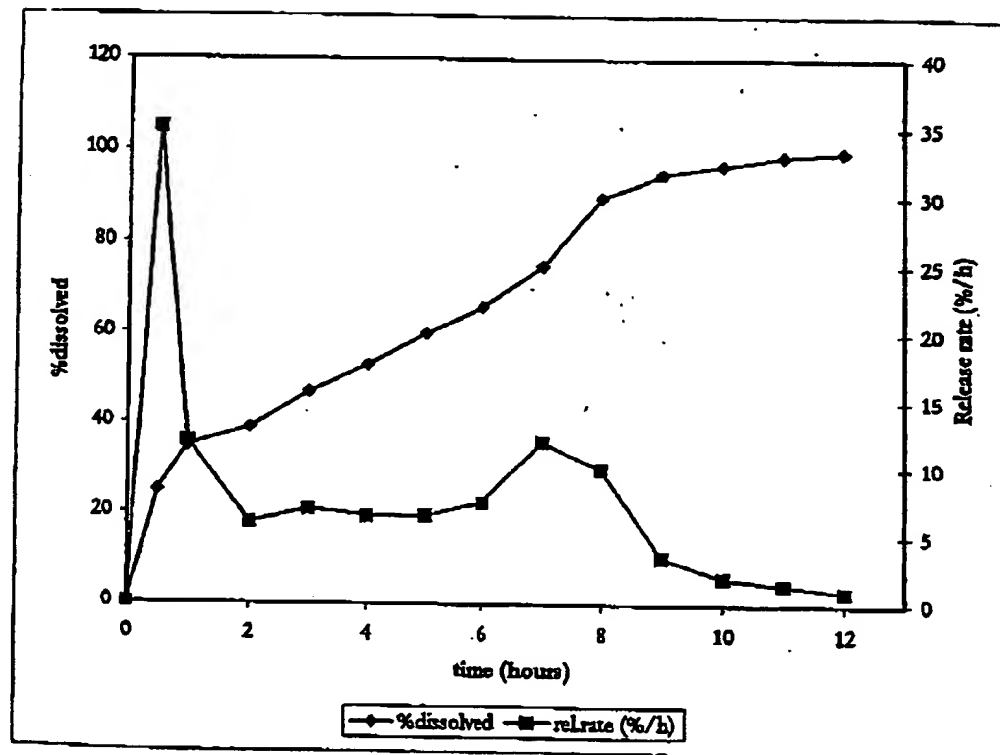


Fig. 5

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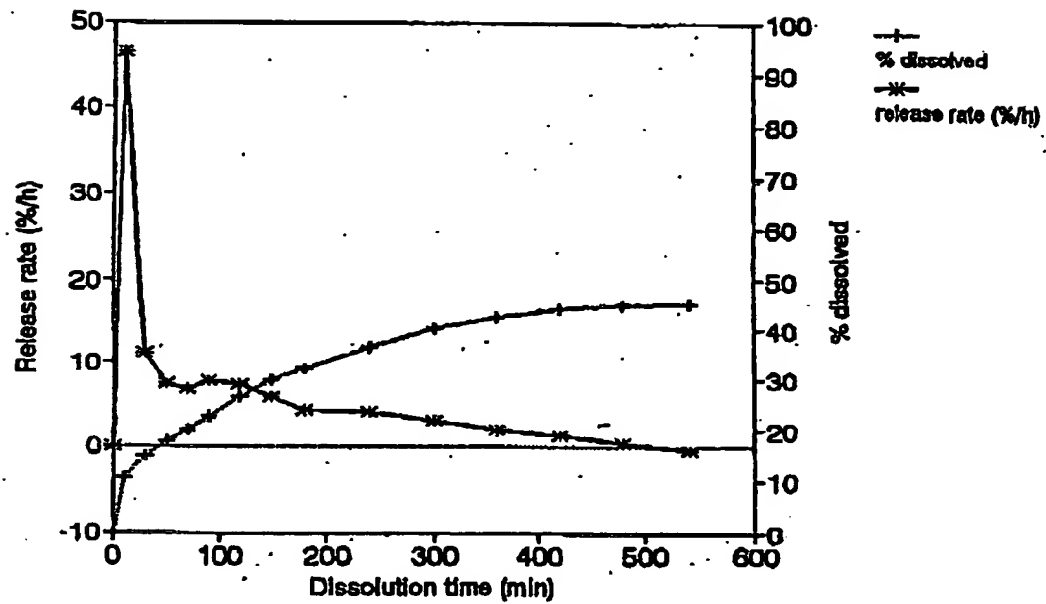


Fig. 6

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Triple compress.CORE+1 layer (94012381)

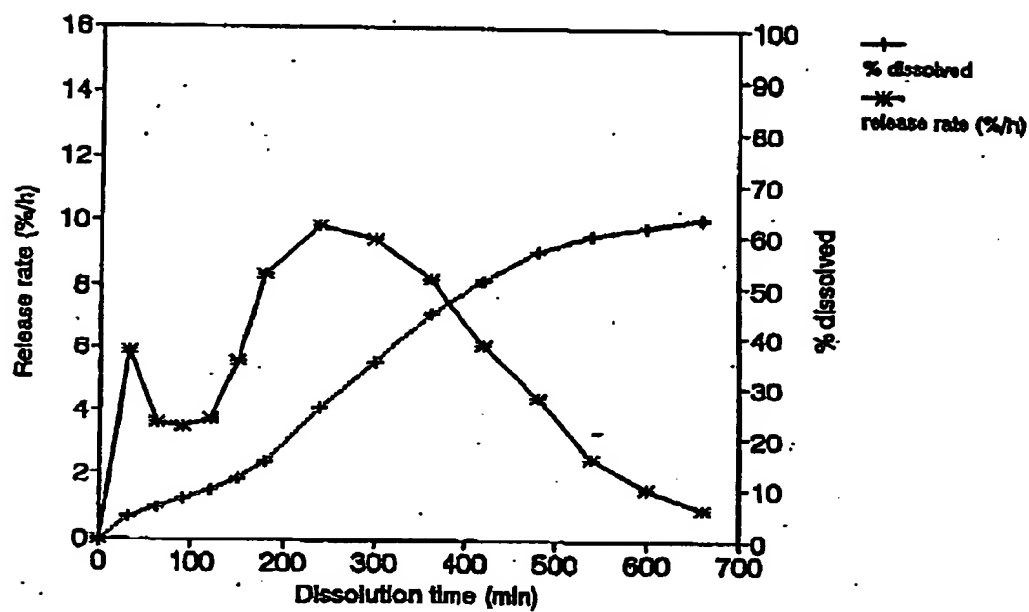


Fig. 7

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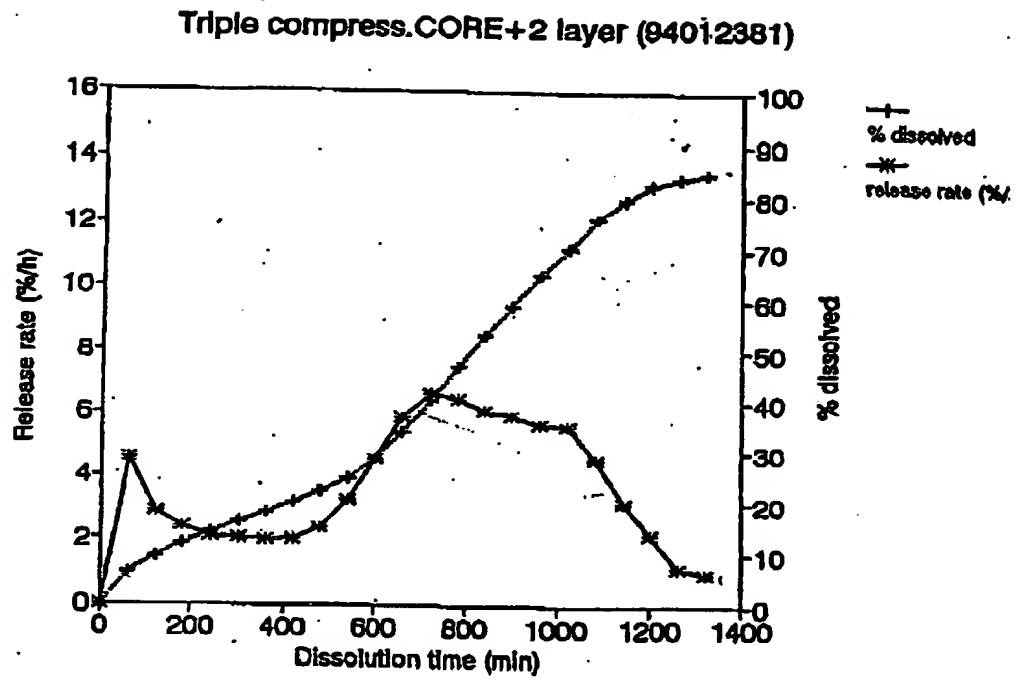


Fig. 8

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Triple compression with coat (94012401)

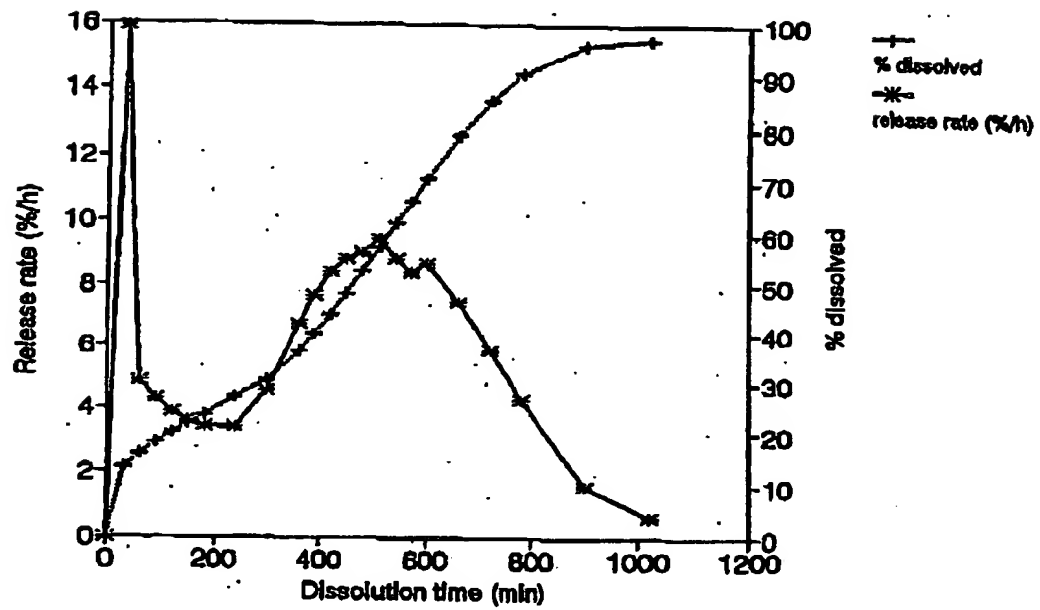


Fig. 9

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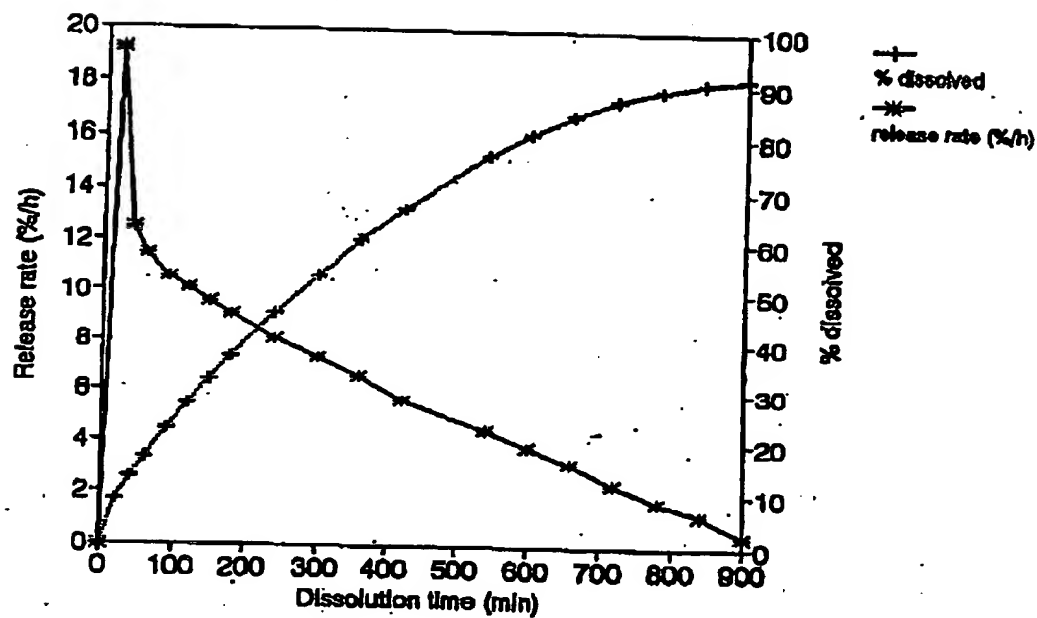


Fig. 10

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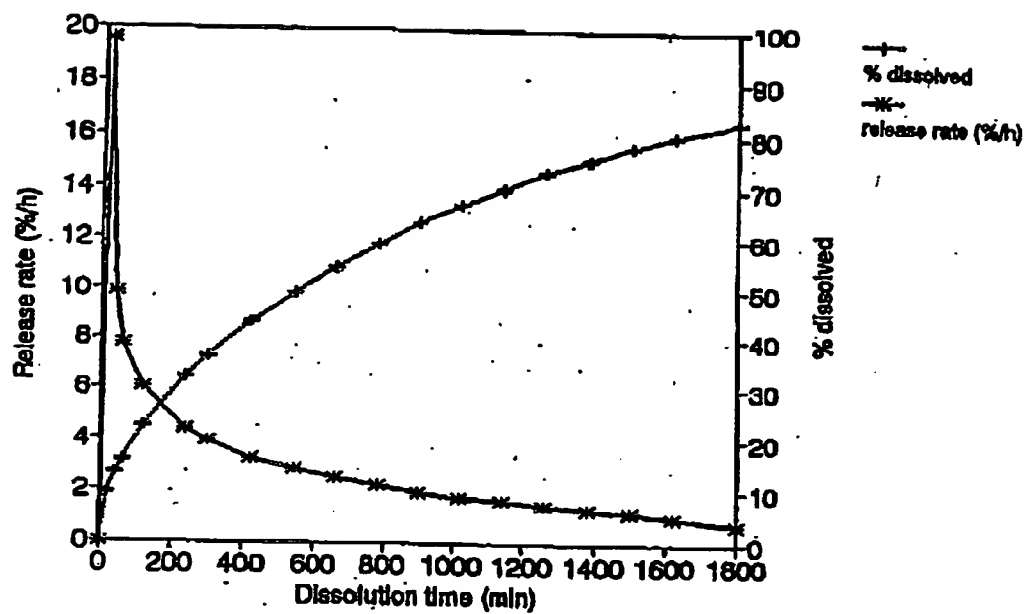


Fig. 11

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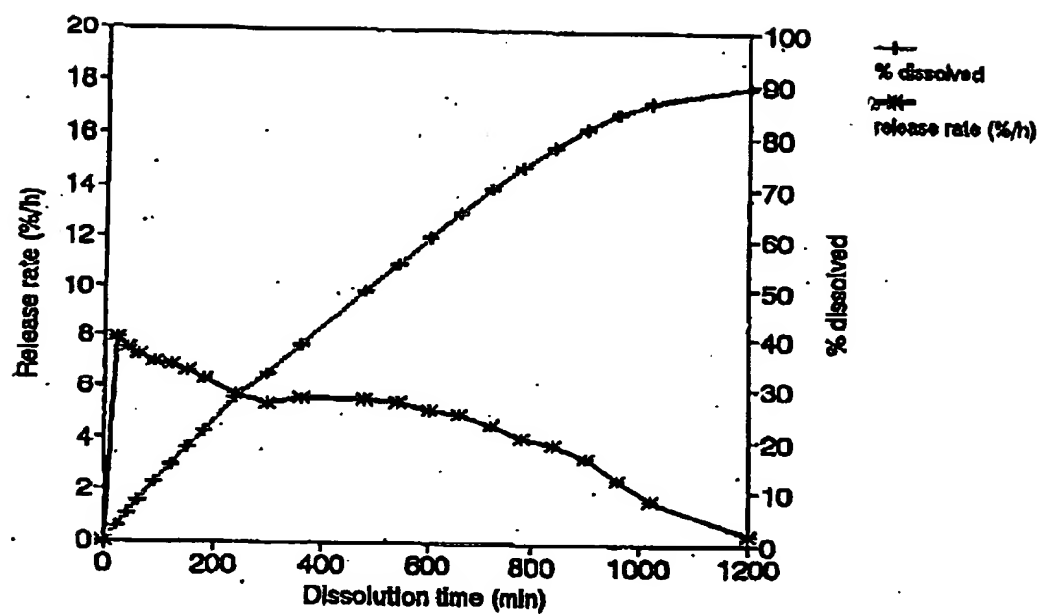


Fig. 12

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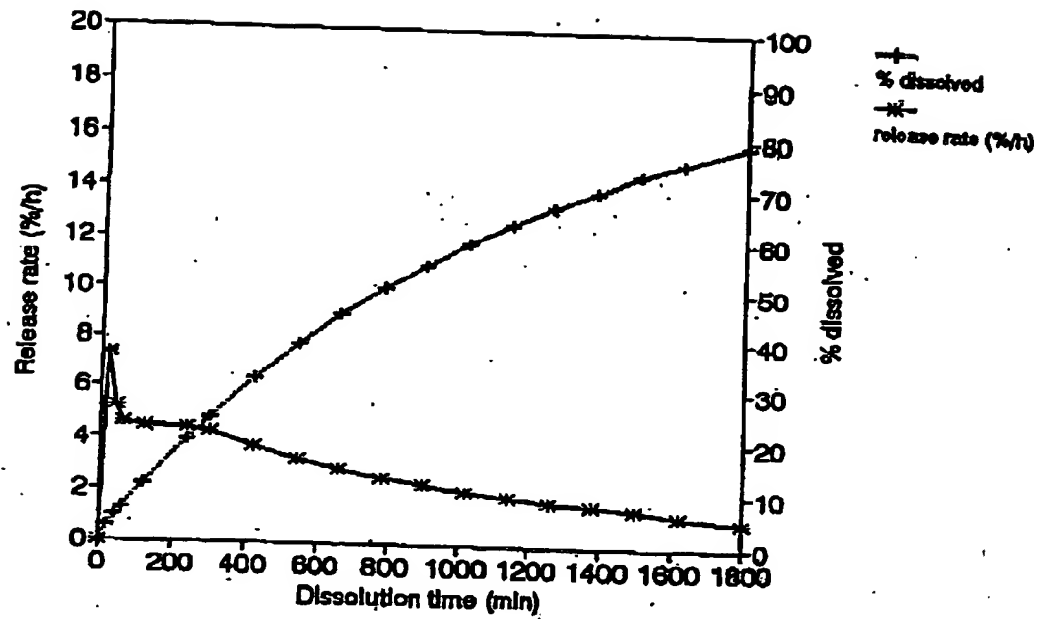


Fig. 13

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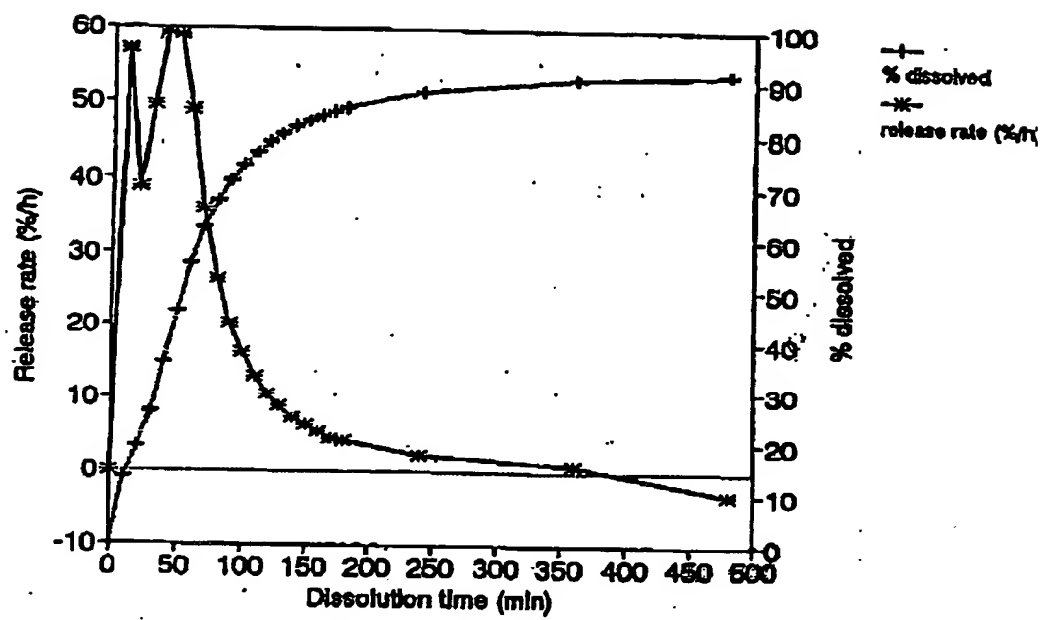


Fig. 14

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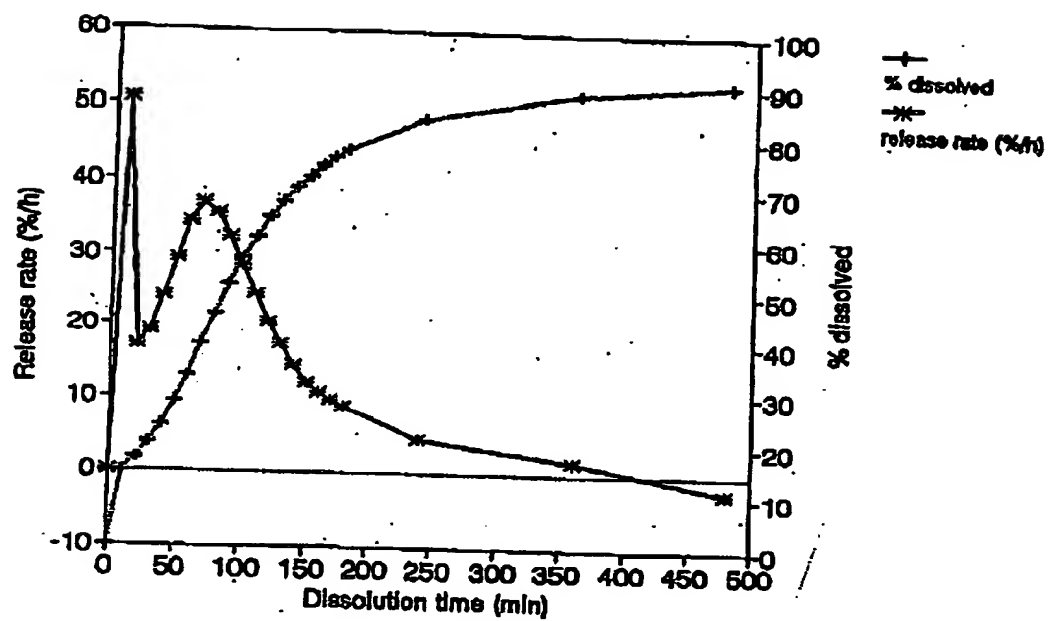


Fig. 15

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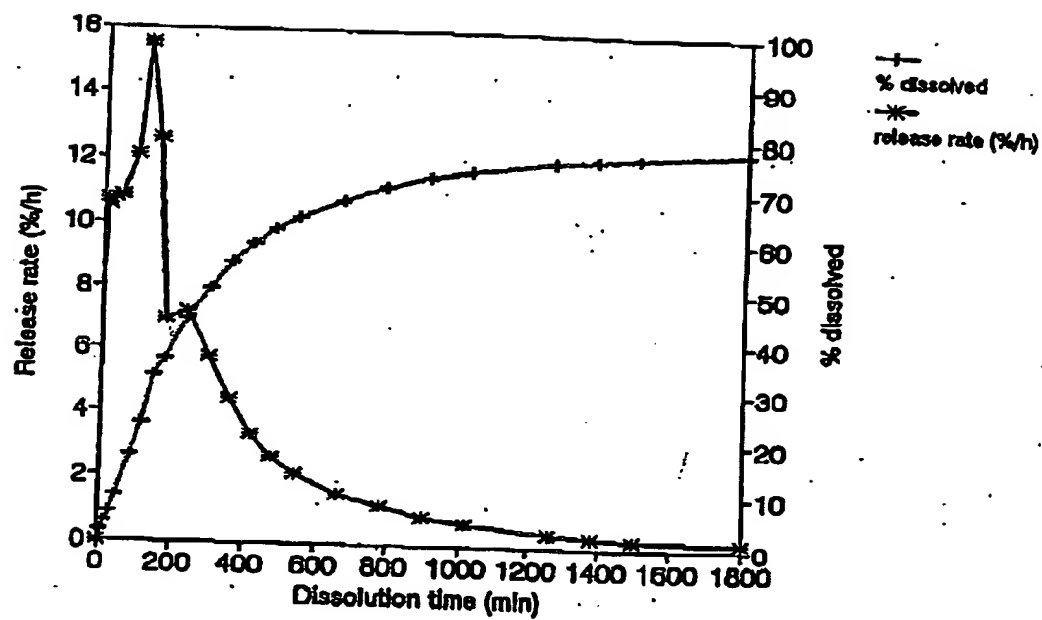


Fig. 16

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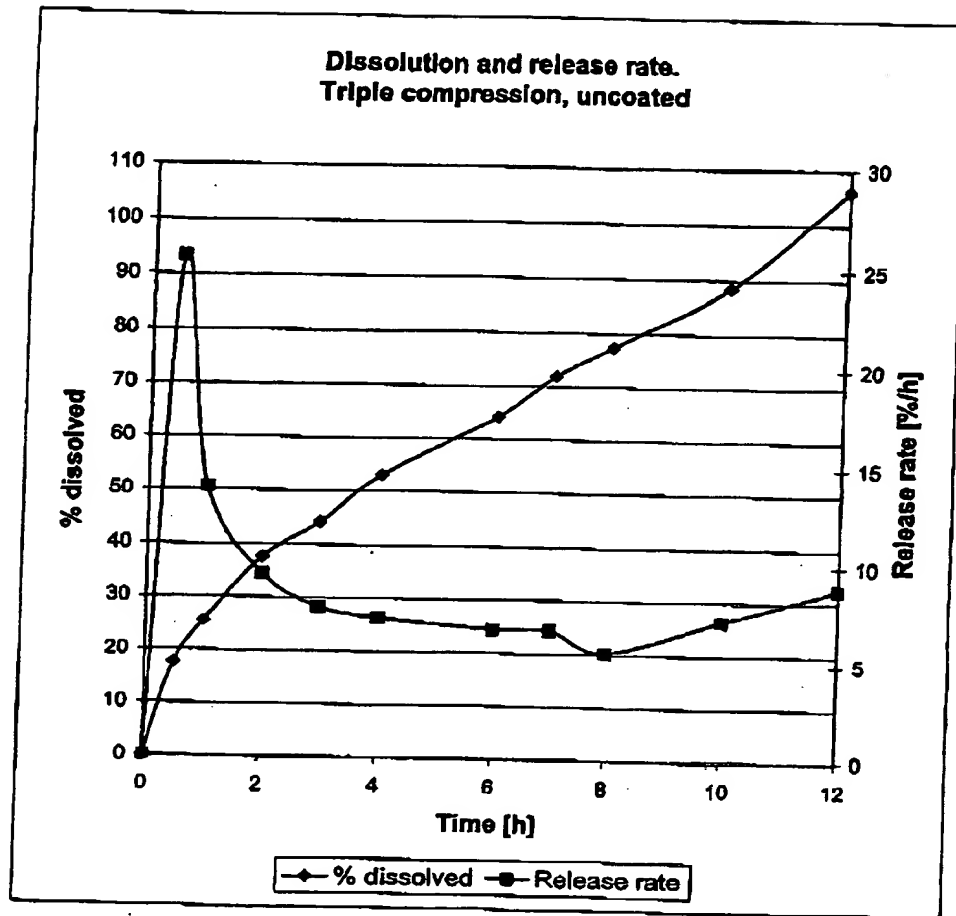


Fig. 17

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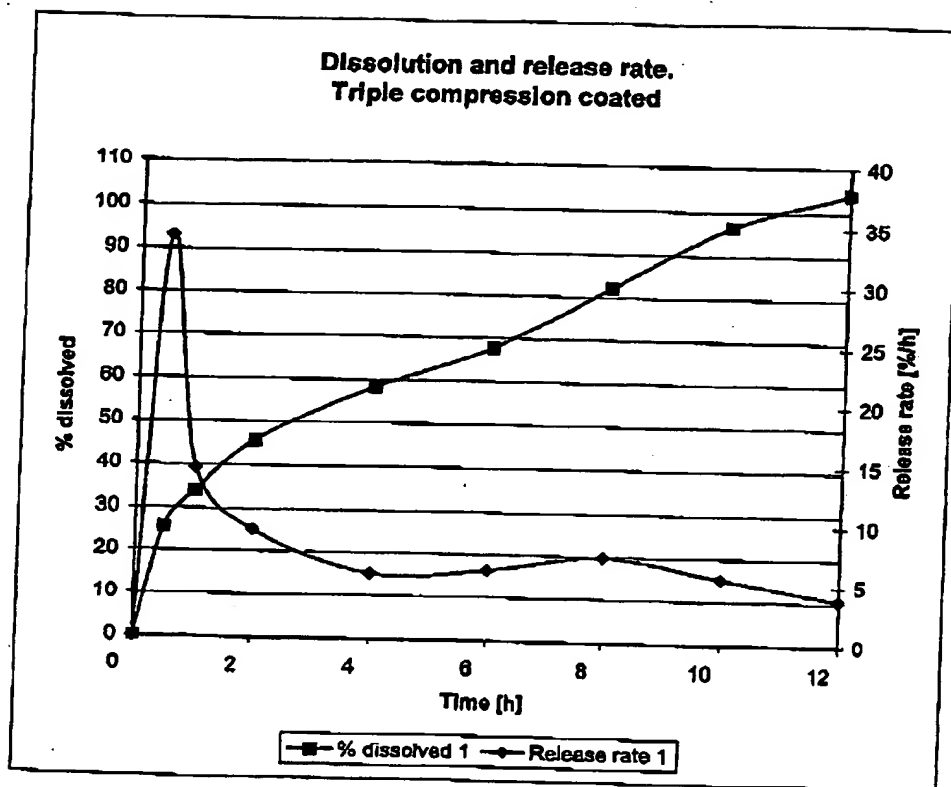


Fig. 18

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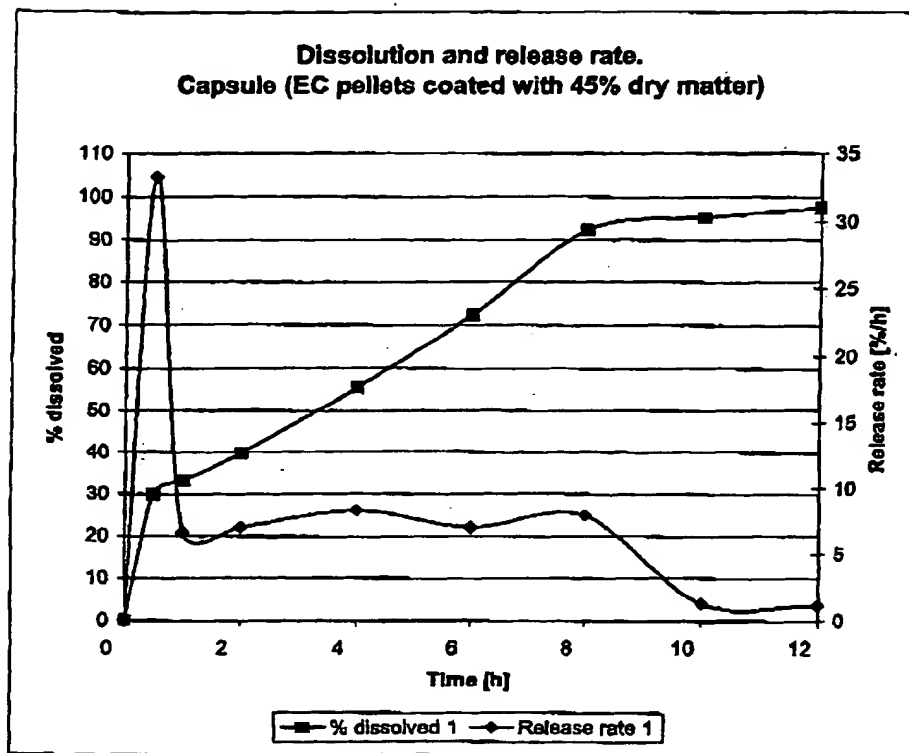


Fig. 19

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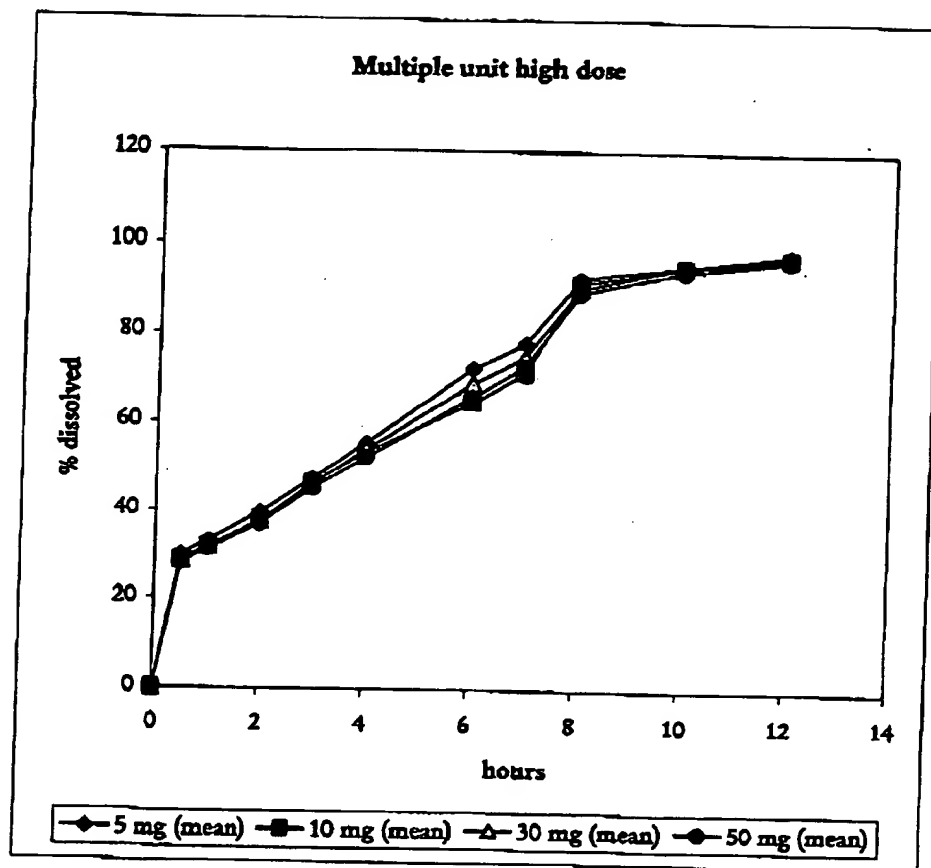


Fig. 20

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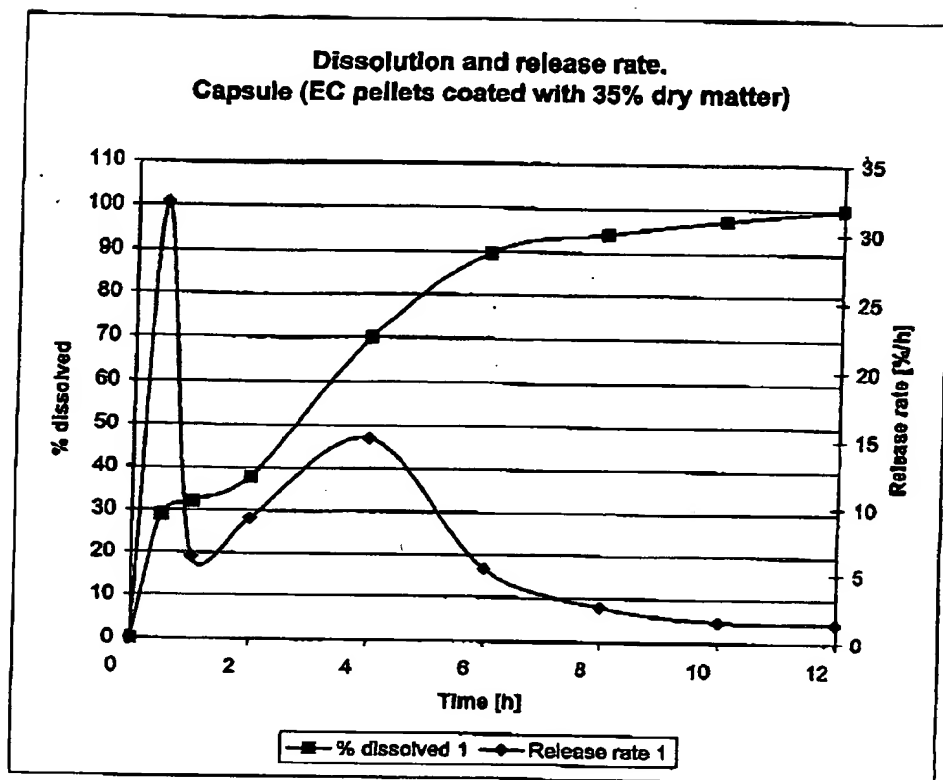


Fig. 21

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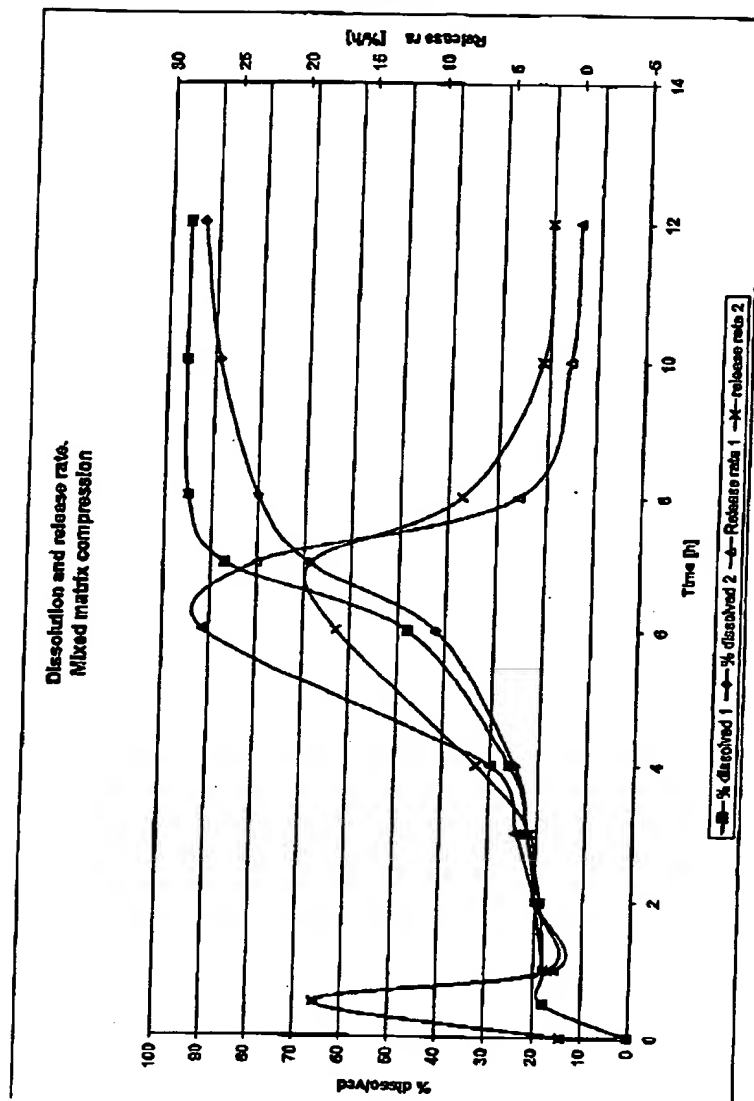


Fig. 22

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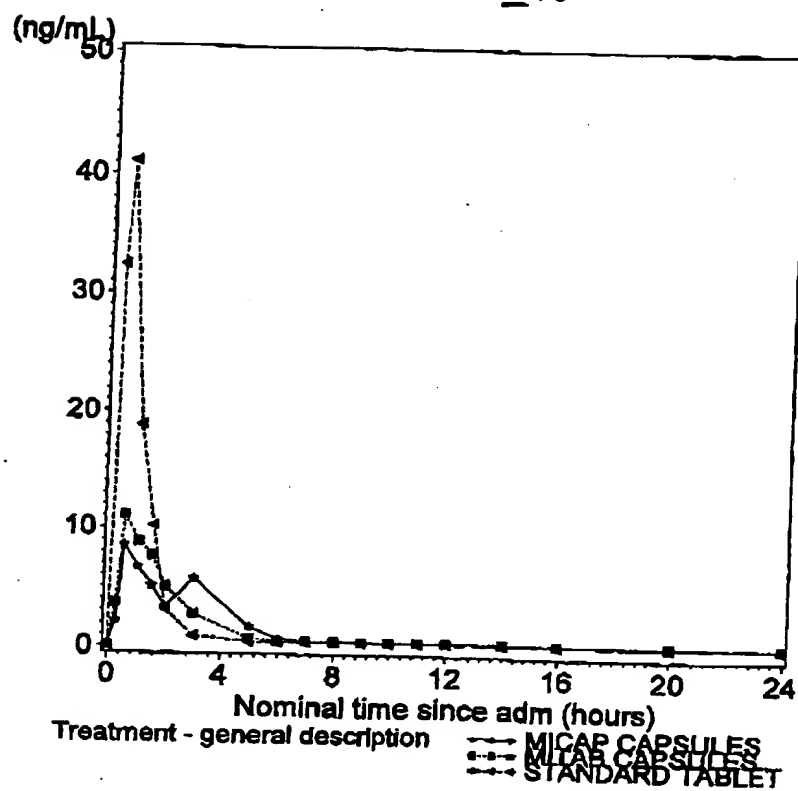


Fig. 23

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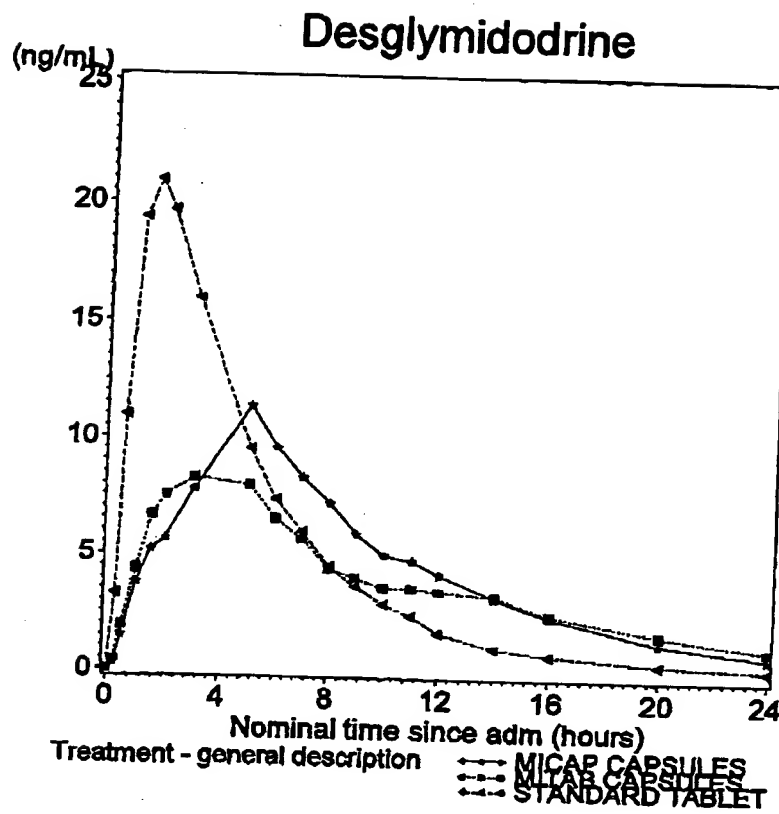


Fig. 24

A COVERBINDER COVER 1-800-366-6050
5/8" PTO-1683 for 121 to 150 sheets

